

320 HECO FC/PIU 11 FEB 2000

FORM PTO-1390
(REV. 1-98)

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

ATTORNEY'S DOCKET NUMBER

TRANSMITTAL LETTER TO THE UNITED STATES
DESIGNATED/ELECTED OFFICE (DO/EO/US)
CONCERNING A FILING UNDER 35 U.S.C. 371

1060-136P

U.S. APPLICATION NO. (If known, see 37 CFR 1.5)

09/485441

INTERNATIONAL APPLICATION NO.

INTERNATIONAL FILING DATE

PRIORITY DATE CLAIMED

PCT/HU98/00076

August 7, 1998

August 12, 1997

TITLE OF INVENTION

1,3-DIOXOLO/4,5-H/2,3/BENZODIAZEPINE DERIVATIVES AS AMPA/KAINATE RECEPTOR INHIBITORS

APPLICANT(S) FOR DO/EO/US

BARKOCZY, Jozsef; CSELENYAK, Judit; RATKAI, Zoltan; SIMIG, Gyula; BALAZS, Laszlo; DOMAN, Imre; KOTAY NAGY, Peter; GREFF, Zoltan; SERES, Peter; SZABO, Geza; GACSALYI, Istvan;***

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39 (1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
 - a. ☒ is transmitted herewith (required only if not transmitted by the International Bureau). WO 99/07708
 - b. ☒ has been transmitted by the International Bureau.
 - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(3)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(2)).
 - a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
 - b. ☐ have been transmitted by the International Bureau.
 - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
 - d. ☒ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98/-1449 and International Search Report (PCT/ISA/210)
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.
☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☒ Other items or information:
 - 1.) International Preliminary Examination Report (PCT/IPEA/409)
 - 2.) PCT Request Form (PCT/RO/101)
 - 3.) Zero (0) sheets of Formal Drawings

*** GIGLER, Gabor; GYERTYAN, Istvan; LEVAY, Gyorgy; KOVACS, Attila; SIMO, Annamaria; SZABADOS, Tamas;
EGYED, Andras; VEGH, Miklos; TIHANYI, Karoly

U.S. APPLICATION NO (if known, see 37 CFR 1.5)

INTERNATIONAL APPLICATION NO

ATTORNEY'S DOCKET NUMBER

09/485441

PCT/HU98/00076

1060-136P

17. ☒ The following fees are submitted:**BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5):**

Neither international preliminary examination fee (37 CFR 1.482)
nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO
and International Search Report not prepared by the EPO or JPO. \$970.00

International preliminary examination fee (37 CFR 1.482) not paid to
USPTO but International Search Report prepared by the EPO or JPO \$840.00

International preliminary examination fee (37 CFR 1.482) not paid to USPTO
but international search fee (37 CFR 1.445(a)(2)) paid to USPTO. \$690.00

International preliminary examination fee (37 CFR 1.482) paid to USPTO
but all claims did not satisfy provisions of PCT Article 33(1)-(4) \$670.00

International preliminary examination fee (37 CFR 1.482) paid to USPTO
and all claims satisfied provisions of PCT Article 33(1)-(4). \$96.00

ENTER APPROPRIATE BASIC FEE AMOUNT =**CALCULATIONS PTO USE ONLY**

\$ 840.00

\$ 130.00

Surcharge of \$130.00 for furnishing the oath or declaration later than ☐ 20 ☒ 30
months from the earliest claimed priority date (37 CFR 1.492(e)).

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE
Total Claims	17 - 20 =	0	X \$18.00
Independent Claims	4 - 3 =	1	X \$78.00

MULTIPLE DEPENDENT CLAIM(S) (if applicable)	Yes	+ \$260.00
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TOTAL OF ABOVE CALCULATIONS =		
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Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28).	
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SUBTOTAL =	\$ 1308.00
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Processing fee of \$130.00 for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(f)).	
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TOTAL NATIONAL FEE =	\$ 1308.00
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Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property +	
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TOTAL FEES ENCLOSED =	\$ 1308.00
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	Amount to be:	\$
	refunded	
	charged	\$

SIGNATURE

WEINER, MARC S.
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REGISTRATION NUMBER

Send all correspondence to:

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/dll February 11, 2000

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416 Rec'd PCT/PTO 11 FEB 2000

PATENT
1060-136P

IN THE U.S. PATENT AND TRADEMARK OFFICE

Applicant: BARKOCZY, Jozsef et al
Int'l. Appl. No.: PCT/HU98/00076
Appl. No.: New Group:
Filed: February 11, 2000 Examiner:
For: 1,3-DIOXOLO/4,5-
H/2,3/BENZODIAZEPINE DERIVATIVES AS
AMPA/KAINATE RECEPTOR INHIBITORS

PRELIMINARY AMENDMENT

BOX PATENT APPLICATION

Assistant Commissioner for Patents
Washington, DC 20231

February 11, 2000

Sir:

The following Preliminary Amendments and Remarks are respectfully submitted in connection with the above-identified application.

AMENDMENTS

IN THE SPECIFICATION:

Please amend the specification as follows:

Before line 1, insert --This application is the national phase under 35 U.S.C. § 371 of PCT International Application No. PCT/HU98/00076 which has an International filing date of August 7, 1998, which designated the United States of America.--

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Docket No. 1060-136P


REMARKS

The specification has been amended to provide a cross-reference to the previously filed International Application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By 

Marc S. Weiner, #32,181

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MSW/d11
1060-136P

(Rev. 01/08/2000)

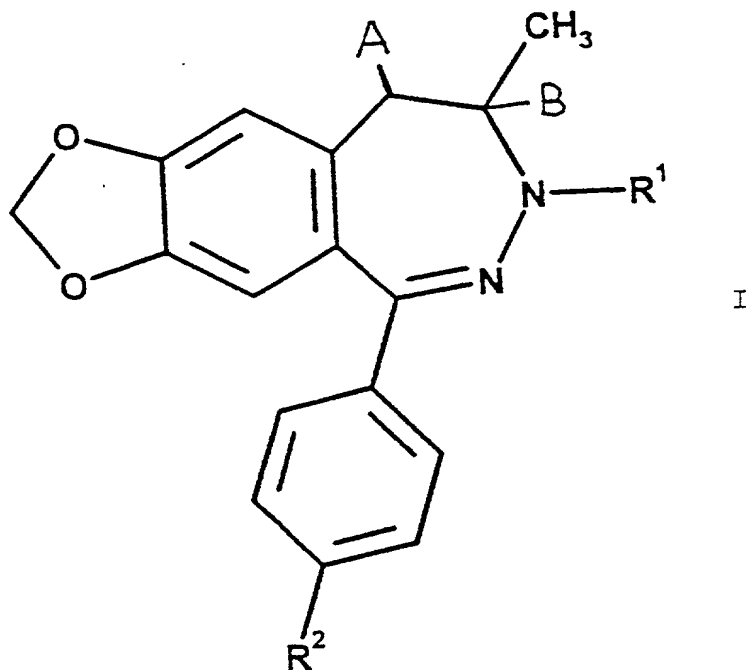
416 Rec'd PCT/PTO 11 FEB 2000

1,3-DIOXOLO[4,5-h][2,3]BENZODIAZEPINE DERIVATIVES AS AMPA/KAINATE RECEPTOR-INHIBITORS

Novel 1,3-dioxolo[4,5-h][2,3]benzodiazepine derivatives, a pharmaceutical composition containing the same, and a process for the preparation of the active ingredient

The invention refers to novel 1,3-dioxolo[4,5-h][2,3]benzodiazepine derivatives, a pharmaceutical composition containing the same, and a process for the preparation of the active ingredient.

More specifically, the invention refers to novel 1,3-dioxolo[4,5-h][2,3]benzodiazepine derivatives of the formula I



wherein

A represents a hydrogen atom,

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B means a hydrogen atom,

R¹ stands for a group of the formula

$-(CH_2)_n-CO-(CH_2)_m-R$, wherein

R represents a halo atom, a pyridyl group or a group of the formula $-NR^3R^4$, wherein R³ and R⁴ mean, independently, a hydrogen

atom, a C₃₋₆ cycloalkyl group, a C₁₋₄ alkoxy group, an amino group, a phenyl group optionally substituted by one or two C₁₋₄ alkyl group(s), a C₁₋₄ alkyl group which latter is optionally substituted by a phenyl group or a saturated heterocyclic group having 5 or 6 members and comprising 1 to 3 nitrogen atom(s) or a nitrogen atom and an oxygen atom as the heteroatom, and said heterocyclic group is optionally substituted by a phenyl group which latter is optionally substituted by 1 to 3 substituent(s), wherein the substituent consists of a C₁₋₄ alkoxy group, or

R³ and R⁴ form, with the adjacent nitrogen atom and optionally with a further nitrogen atom or an oxygen atom, a saturated or unsaturated heterocyclic group having 5 or 6 members, being optionally substituted by a phenyl group that is optionally substituted by 1 to 3 substituents, wherein the

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- substituent is a C₁₋₄ alkoxy group,
n has a value of 0, 1 or 2,
m has a value of 0, 1 or 2, or
- A forms together with B a valence bond
between the carbon atoms in positions
8 and 9, and in this case
- R¹ represents a group of the formula
-CO-(CH₂)_p-R⁶, wherein
R⁶ stands for a halo atom, a phenoxy group,
a C₁₋₄ alkoxy group or a group of the
formula -NR⁷R⁸, wherein
R⁷ and R⁸ mean, independently, a hydrogen
atom, a guanyl group, a C₃₋₆ cyclo-
alkyl group or a C₁₋₄ alkyl group
which latter is optionally substituted
by a phenyl group or a saturated
heterocyclic group having 5 or 6
members and comprising one or more
nitrogen atom(s) or a nitrogen and
an oxygen atom as the heteroatom,
wherein the phenyl group is optionally
substituted by 1 to 3 identical or
different substituent(s), wherein
the substituent is a C₁₋₄ alkoxy
group, or
- R⁷ and R⁸ form together with the adjacent
nitrogen atom an oxopyrrolidinyl
group, a phthalimido group which
latter is optionally substituted,
or a saturated heterocyclic group
having 5 or 6 members and comprising
one or more nitrogen atom(s) or a

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AMPA/kainate receptors play an important role in the acute and chronic diseases of the central nervous system. Through the inhibition of these receptors, muscle relaxant, neuro-protective and anticonvulsive effects can be achieved /Vizi, E.S. et al., CNS Drug Reviews, 2, 91-126 (1996); Lees, G.L., CNS Drugs, 5, 51-74 (1996)/.

The aim of the invention is to prepare novel 2,3-benzodiazepine derivatives that are more effective and less toxic, respectively, than the known 2,3-benzodiazepine derivatives.

It was found that the above aim is achieved by the novel 1,3-dioxolo/4,5-h//2,3/-benzodiazepine derivatives which have - due to their non-competitive AMPA/kainate effect - considerable muscle relaxant, neuroprotective and anticonvulsive activities. Thus, the novel compounds can be employed for the treatment of any diseases (such as epilepsy, diseases resulting in muscle spasm, various neurodegenerative diseases. stroke,) in which the inhibition of the AMPA/kainate receptors is favourable.

In the description and Claims, in the definition of the substituents, under a halo atom primarily a fluoro, chloro, bromo or iodo atom, preferably a fluoro or a chloro atom is meant.

A C₁₋₄ alkyl group is a methyl, ethyl, n-propyl, isopropyl, n-butyl, sec.-butyl,

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tert.-butyl or isobutyl group. Preferably, a C₁₋₄ alkyl group is a methyl, an ethyl or an isopropyl group.

A C₁₋₄ alkoxy group is, primarily, a methoxy, ethoxy, n-propoxy, isopropoxy or n-butoxy group, preferably a methoxy group.

A C₁₋₄ alkanoyl group is, primarily, a formyl, acetyl or n-propionyl group. Preferably, a C₁₋₄ alkanoyl group is an acetyl or a propionyl group.

A C₃₋₆ cycloalkyl group is a cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl group, preferably a cyclopropyl group.

A saturated heterocyclic group having 5 or 6 members and comprising 1 to 3 nitrogen atom(s) or a nitrogen atom and an oxygen atom as the heteroatom is preferably a pyrrolidinyl, piperidinyl, piperazinyl, imidazolyl, triazolyl or morpholino group.

Suitably, the other nitrogen atom of the piperazinyl group is substituted.

In the definition of R³ and R⁴, wherein, together with the adjacent nitrogen atom, they form a saturated or unsaturated heterocyclic group having 5 or 6 members, said group is a heterocyclic group that comprises one or two nitrogen atom(s) or a nitrogen atom and an oxygen atom as the heteroatom, and the heterocyclic ring contains no double bond or it contains one or more double bond(s). The nitrogen atom or one of the nitrogen atoms of the heterocyclic group

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is attached to the carbonyl group in the definition of R^1 . Such a heterocyclic group is, for example, a pyrrolidinyl, piperidinyl, pyridyl, morpholino, piperazinyl etc. group. Preferably, the above heterocyclic group is a pyrrolidinyl, pyridinyl, morpholino or piperazinyl group. Especially preferably, said heterocyclic group is a piperazinyl group. Suitably, the other nitrogen atom of the piperazinyl group is substituted.

Under a pharmaceutically suitable acid addition salt an acid addition salt formed with a pharmaceutically suitable inorganic acid such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid etc. or with a pharmaceutically suitable organic acid such as formic acid, acetic acid, fumaric acid, maleic acid, lactic acid, malic acid, tartaric acid, succinic acid, citric acid, methanesulfonic acid etc. is meant.

The invention includes any isomers of the compounds of the formula I and the mixtures thereof.

Under the isomers of the compounds of the formula I - due to the presence of at least one chiral centre - both enantiomers, and - because of isomerisms that exist in case of certain substitutions - the isomers E and Z, diastereomers, tautomeric forms, and the mixtures thereof such as the racemate are meant.

A preferred subgroup of the compounds

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of the formula I consists of the 7,8-dihydro-
-8-methyl-9H-1,3-dioxolo/4,5-h//2,3/benzo-
diazepine derivatives and pharmaceutically
suitable acid addition salts thereof, wherein

A represents a hydrogen atom,

B means a hydrogen atom,

R¹ stands for a group of the formula

$-(CH_2)_n-\dot{C}O-(CH_2)_m-R$, wherein

R represents a chloro atom, a pyridyl
group or a group of the formula $-NR^3R^4$,
wherein

R³ and R⁴ mean, independently, a hydrogen
atom, a cyclopropyl group, a C₁₋₄ alkoxy
group, an amino group, a phenyl group
optionally substituted by one or two
methyl group(s) or a C₁₋₄ alkyl group
which latter is optionally substituted
by a phenyl group or a saturated
heterocyclic group having 5 or 6 members
and comprising 1 to 3 nitrogen atom(s)
or a nitrogen atom and an oxygen atom
as the heteroatom, and the heterocyclic
group is optionally substituted by a
phenyl group which latter is optionally
substituted by 1 to 3 methoxy groups,

or

R³ and R⁴ form, with the adjacent
nitrogen atom and optionally with a
further nitrogen atom or an oxygen atom,
a saturated or unsaturated heterocyclic
group having 5 or 6 members, being
optionally substituted by a phenyl group

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that is optionally substituted by 1
to 3 methoxy groups, n has a value of
0, 1 or 2,

m has a value of 0, 1 or 2,

R² stands for a nitro group or an amino group.

Within the above subgroup, suitable 7,8-
-dihydro-8-methyl-9H-1,3-dioxolo/4,5-h//2,3/-
benzodiazepine derivatives are the following
compounds of the formula I, wherein

R³ and R⁴ represent, independently, a hydrogen
atom, a cyclopropyl group, a methoxy group,
an amino group, a dimethylaminophenyl group
or a C₁₋₂ alkyl group which latter is
substituted by a phenyl, morpholino or
piperazinyl group, wherein the piperazinyl
group is substituted by a methoxyphenyl
group, or

R³ and R⁴ form, together with the adjacent
nitrogen atom and optionally a further
nitrogen atom or oxygen atom, an imidazolyl,
morpholino or piperazinyl group, wherein
the piperazinyl group is substituted by
a methoxyphenyl group,

n has a value of 0 or 1,

m has a value of 0 or 1,

R² stands for a nitro group or an amino group,

A represents a hydrogen atom,

B means a hydrogen atom,

and pharmaceutically suitable acid addition
salts thereof.

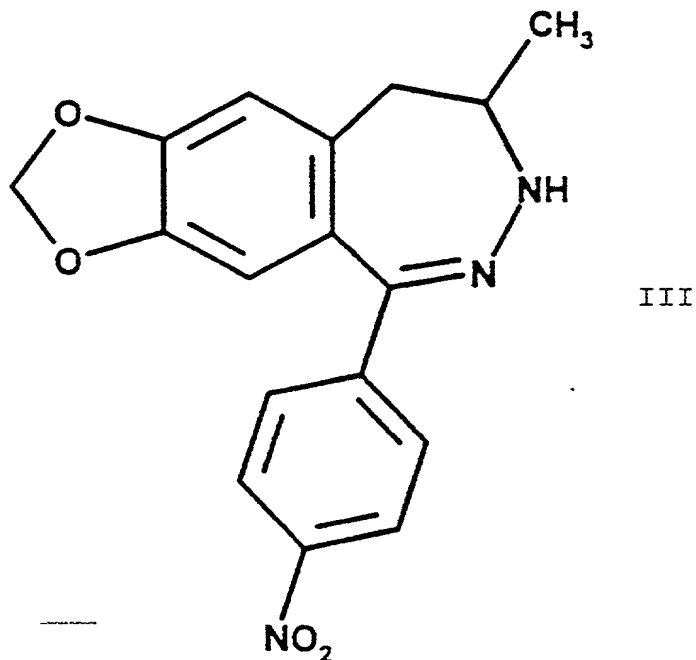
The especially preferred 7,8-dihydro-
-8-methyl-9H-1,3-dioxolo/4,5-h//2,3/benzo-

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R^1 , A and B are as defined in connection with the latter subgroup, and pharmaceutically suitable acid addition salts thereof.

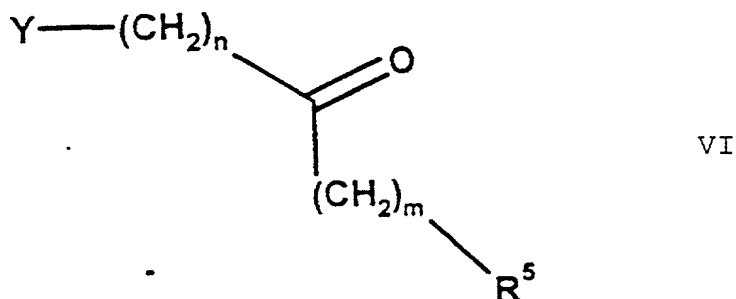
The 1,3-dioxolo/4,5-h//2,3/benzodiazepine derivatives of the formula I are prepared as follows:

a) for the preparation of a compound of the formula I, wherein R^1 represents a group of the formula $-(CH_2)_n-CO-(CH_2)_m-R$, wherein R stands for a halo atom or a pyridyl group, n has a value of 0, 1 or 2, m has a value of 0, 1 or 2, R^2 means a nitro group, A and B represent a hydrogen atom, the 7,8-dihydro-8-methyl-5-(4-nitrophenyl)-9H-1,3-dioxolo/4,5-h//2,3/benzodiazepine of the formula III



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is reacted with a reagent of the formula VI



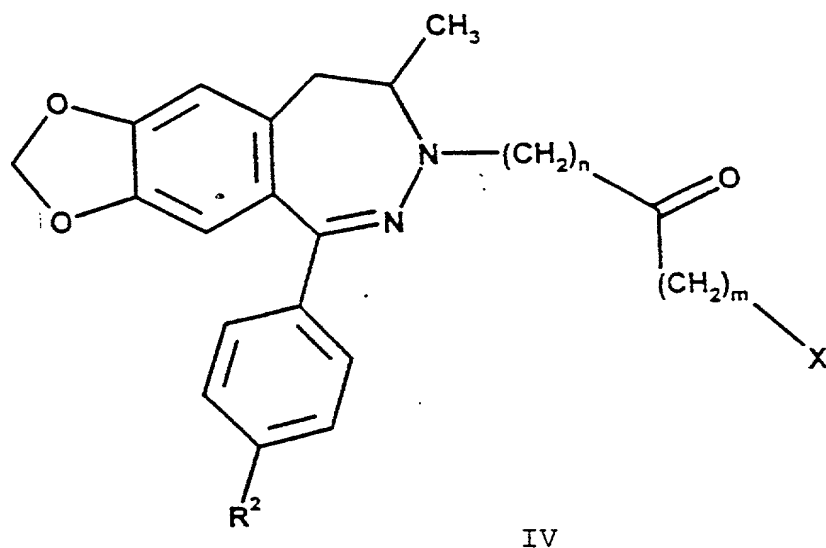
wherein Y represents a leaving group, R^5 is a halo atom or a pyridyl group; or

b) for the preparation of a compound of the formula I, wherein R^1 represents a group of the formula $-(\text{CH}_2)_n-\text{CO}-(\text{CH}_2)_m-\text{R}$, wherein R stands for an imidazolyl group, n has a value of 0, m has a value of 0, R^2 means a nitro group, A and B represent a hydrogen atom, the 7,8-dihydro-8-methyl-5-(4-nitrophenyl)-9H-1,3-dioxolo[4,5-h//2,3/-benzodiazepine of the formula III is reacted with 1,1'-carbonyldiimidazole; or

c) for the preparation of a compound of the formula I, wherein R^1 represents a group of the formula $-(\text{CH}_2)_n-\text{CO}-(\text{CH}_2)_m-\text{R}$, wherein R stands for a group of the formula $-\text{NR}^3\text{R}^4$, wherein R^3 , R^4 , n and m are as defined in connection with formula I, R^2 means a nitro group, A and B represent a hydrogen atom, the 7,8-dihydro-8-methyl-5-(4-nitrophenyl)-9H-1,3-dioxolo[4,5-h//2,3/-benzodiazepine of the formula III is reacted with a reagent of the formula VI, wherein Y and R^5 represent,

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independently, a leaving group, n and m are as stated above, and the obtained benzodiazepine derivative of the formula IV



wherein X stands for a leaving group, n and m are as stated above, is reacted with an amine of the formula VII

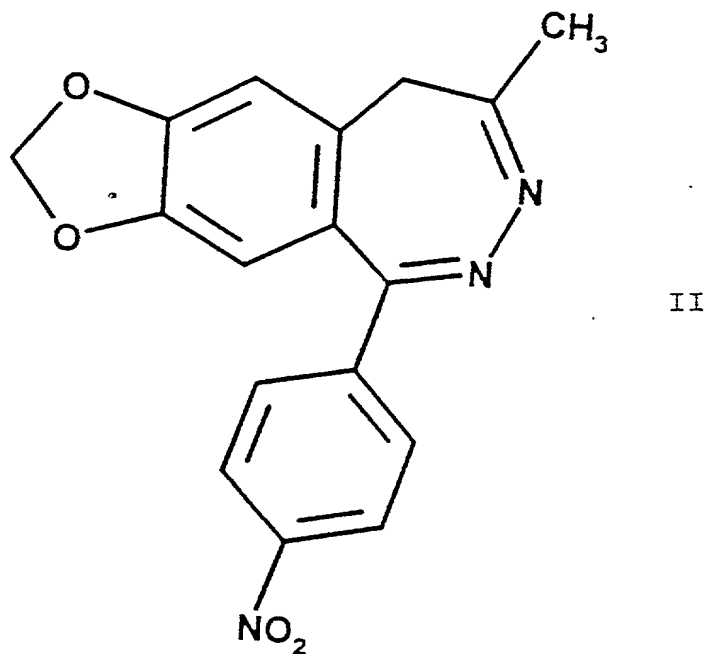


wherein R³ and R⁴ are as stated above; or

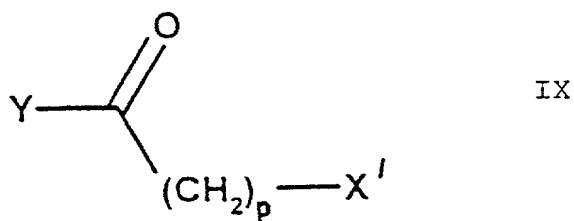
d) for the preparation of a compound of the formula I, wherein R¹ stands for a group of the formula -CO-(CH₂)_p-R⁶, wherein R⁶ represents a halo atom, a phenoxy group or a C₁₋₄ alkoxy group, p has a value of 0, 1 or 2, A forms together with B a valence bond, R² means a nitro group, the 8-methyl-

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-5-(4-nitrophenyl)-9H-1,3-dioxolo[4,5-h][2,3]-
benzodiazepine of the formula II



is reacted with an acylating agent of the
formula IX



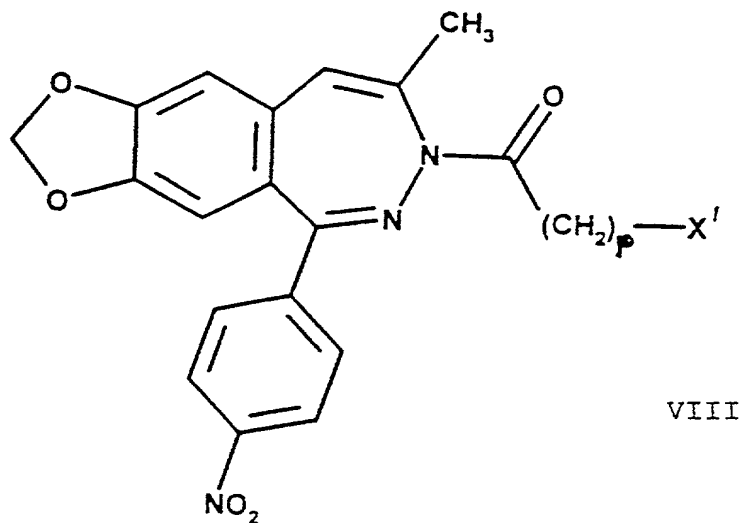
wherein Y represents a leaving group, X' stands
for a halo atom, a phenoxy group or a C₁₋₄
alkoxy group, p has a value of 0, 1 or 2;
or

e) for the preparation of a compound
of the formula I, wherein R¹ stands for a

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group of the formula $-\text{CO}-(\text{CH}_2)_p-\text{R}^6$, wherein R^6 represents a group of the formula $-\text{NR}^7\text{R}^8$, wherein R^7 , R^8 and p are as defined in connection with the formula I, A forms together with B a valence bond, R^2 means a nitro group, the 8-methyl-5-(4-nitrophenyl)-9H-1,3-dioxolo-/4,5-h//2,3/benzodiazepine of the formula II is reacted with an acylating agent of the formula IX, wherein each of Y and X' represents, independently, a leaving group, p is as stated above, and the obtained acylated compound of the formula VIII



VIII

wherein X' and p are as defined above, is reacted with an amine of the formula HNR^7R^8 , wherein R^7 and R^8 are as stated above;

and, if desired, an obtained compound of the formula I, wherein R^2 represents a nitro group, $-\text{R}^1$, A and B are as defined in connection with the formula I, is transformed

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into a compound of the formula I, wherein R^2 stands for an amino group, by reduction;

and, if desired, an obtained compound of the formula I, wherein R^2 represents an amino group, R^1 , A and B are as defined in connection with the formula I, is reacted with a C_{1-4} alkanecarboxylic acid or a reactive acylating derivative thereof;

and, if desired, an obtained base of the formula I is converted to a pharmaceutically suitable acid addition salt or liberated from the acid addition salt.

If a reagent of the formula VI, wherein n has a value of 0, is used, said reagent is an acylating agent such as a carboxylic halide, a carboxylic anhydride, a carbonate ester, carbonyldiimidazole, an omega-halo-carboxylic halide, an omega-halocarbonate ester etc. The acylation is carried out in the presence or absence of an acid binding agent and/or pyridine, at a temperature of -20 to $+150$ °C, in the presence or absence of an organic solvent.

If a reagent of the formula VI, wherein n has a value of 1 or 2, is used, said reagent is an alkylating agent, for example the corresponding halide. The alkylation is performed in the presence or absence of an acid binding agent, at a temperature of 20 to 200 °C, in the presence or absence of an organic solvent.

The reaction of the benzodiazepine

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derivative of the formula IV and the amine of the formula VII is carried out in a manner known from the literature /Houben-Weyl: Methoden der Organischen Chemie, Band XI, Amine, G. Thieme Verlag, Stuttgart, 1957; S. Patai: The chemistry of amine group, Interscience Publishers, 1968/.

The acylation of the compound of the formula II with the acylating agent of the formula IX and the amination of the compound of the formula VIII with the amine of the formula HNR^7R^8 are performed in a similar manner as described above.

The nitro compounds of the formula I can be reduced in a manner known in itself to obtain the corresponding amino compound. The reduction can be carried out for example with tin(II) chloride or in the presence of a catalyst using a hydrogen source. For example, the catalyst can be Raney nickel, palladium or platinum oxide, the hydrogen source is, for example, hydrazine, hydrazine hydrate, formic acid, a trialkylammonium formate or an alkali metal formate.

If desired, a base of the formula I is reacted with an inorganic or organic acid to transform it into a pharmaceutically suitable acid addition salt, or the base of the formula I is liberated from the acid addition salt using a stronger base.

The starting compound 7,8-dihydro-8-methyl-5-(4-nitrophenyl)-9H-1,3-dioxolo-

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/4,5-h//2,3/benzodiazepine of the formula III can be prepared by reducing 8-methyl-5-(4-nitrophenyl)-9H-1,3-dioxolo/4,5-h//2,3/-benzodiazepine of the formula II in an analogous manner as described in the literature /Houben-Weyl: Methoden der Organischen Chemie, Band IV, Reduktion, G. Thieme Verlag, Stuttgart, 1989/ or using the processes known from HU-P No. 186 760.

The compound of the formula II can be prepared by the process known from HU-P No. 191 702.

The reagents of the formulae VI and IX as well as the amines of the formulae VII and HNR^7R^8 are commercially available.

The pharmacological effect of the novel compounds of the formula I was studied by in vitro and in vivo methods. 8-Methyl-5-(4-aminophenyl)-9H-1,3-dioxolo/4,5-h//2,3/benzodiazepine (compound "A") known from HUP No. 191 698 and GB-P No. 2 162 184 was used as the reference substance.

In vitro determination of AMPA antagonist effect

PSI (inhibition of population spike)
test

The field potentials (population spike) evoked by electric stimulation of the Shaffer collateral commissural pathway were measured in the CA1 neurones of rat hippocampus. The

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population spike can be inhibited by AMPA/kainate antagonists. The non-cumulative IC_{50} values are shown in Table I. /Tarnawa, I., Molnár, P., Gaál, L., Andrási, F.: Inhibition of hippocampal field potentials by GYKI 52466 in vitro and in vivo, Acta Physiol. Hung., 79(2), 163-9 (1992)/.

SD (spreading depression) test

The method is based on the phenomenon of spreading depression evoked by kainate in isolated retinal preparation of the chicken. The formation of spreading depression is inhibited (delayed) by AMPA/kainate antagonists. /Sheardown M.J.: The triggering of spreading depression in the chicken retina: a pharmacological study, Brain Res., 607(1-2), 189-194 (1993)/. The obtained IC_{50} values are shown in Table I.

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Table I

Results obtained in tests suitable for the determination of in vitro AMPA antagonist effect

Compound (No. of Example)	Percent inhibition of population spike (10 microM)	SD ^a IC ₅₀ in microM
16	100	1.3
17	95	1.5
19	95	no data
46	no data	6.5
61	no data	2.8
"A"	58	9.5

^a

Spreading depression test.

As shown in Table I, the inhibitory effects of the novel compounds are significantly higher than that of reference compound "A".

In vivo assays

Muscle relaxant effect

The assay was done according to Hoppe in male NMRI mice weighing 20 to 25 g, with 10 animals in each group /Hoppe, J.O., J. Pharmacol. Exp. Ther., 100, 333 (1950)/. Following the ip. treatment of animals, the number of mice showing muscle weakness were

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recorded at every 10 minutes in the first hour and at half hour intervals afterwards. The animals falling off the 60° inclined screen within 30 seconds were considered positive. ED₅₀ values of the given compounds were determined at each time. The duration of effect was defined as the time of last reading when the effect was at least 30 %. The results obtained are summarized in Table II.

Table II
Muscle relaxant effect

Compound (No. of Example)	Muscle relaxant effect	
	ED ₅₀ ^x ip. in mg/kg	duration in hr
16	21.1	higher than 2
17	18.1	4
"A"	24.5	1

^x determined at the time of maximal effect.

Although the muscle relaxant activity of the novel compounds are about the same as that of reference compound "A", the duration of action is significantly longer as shown in Table II.

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Maximal electroshock test (MES)

Male NMRI mice weighing 20 to 30 g were used for the method of Swinyard et al. /Swinyard, E.A., Brown, W.C. and Goodman, L.S.: Comparative assays of antiepileptic drugs in mice and rats, J. Pharmacol., 106, 319 (1952)/. The animals, 10 in each group, were treated ip. either with various doses of the test substance or with vehicle. After 30 minutes, a 50 Hz, 40 mA electroshock was applied for 0.4 s through corneal electrodes. The number of animals that developed tonic extensor convulsion of the hind-limbs was registered, percent inhibition was calculated, and ED₅₀ values were determined by the method of Litchfield and Wilcoxon /Litchfield, J.T., Wilcoxon, F.A.: A simplified method of evaluating dose-effect experiments, J. Pharmacol. Exp. Ther., 96, 99 (1949)/ and summarized in Table III.

Audiogenic seizure (AS) test

The experiments were carried out by the slightly modified method of De Sarro et al. /De Sarro, G.B., Croucher, M.J. and Meldrum, B.S.: Anticonvulsant action of DS 103-282, Neuropharm., 23, 525 (1984)/. Groups of 8 male DBA/2j strain mice weighing 7 to 14 g were treated ip. with the test substance in 10 ml/kg volume. 15 minutes later, the animals

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were placed into a covered glass container (30 cm in diameter) and exposed to a 14 kHz 120 dB tone for 60 s at the most. Seizure response was assessed using the following scale: 0 = normal behaviour, 1 = wild running, 2 = clonus, 3 = tonic flexor seizure, 4 = tonic extensor seizure. The maximum response during the 60 s exposure was recorded for each animal. Lethality was also noted. The ED₅₀ values were determined by the method of Litchfield and Wilcoxon concerning the inhibition of clonic seizures and tonic extensor convulsions. The results are summarized in Table III.

Table III
Anticonvulsant effect following ip. treatment

Compound (No. of Example)	MES ^x ED ₅₀ in mg/kg	AS ^{xx}	
		tonic convulsion	clonic
16	4.6	1.6	2.5
17	3.7	no data	no data
"A"	6.9	3.6	4.3

^x Inhibition of maximal electroshock.

^{xx} Inhibition of sound induced seizure.

The novel compounds are significantly more

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effective at the inhibition of maximal electroshock and audiogenic seizure than the reference compound "A" as shown in Table III.

The compound of Example 46 has an approximate anticonvulsive ED_{50} value of 10 mg/kg ip. in the MES test (not shown in Table III), while in 60 mg/kg dose it has no muscle relaxant effect in the inclined screen. In contrast, the anticonvulsive ED_{50} value of the reference compound "A" is 6.9 mg/kg, however, at about 4.5 times higher dose, the reference compound produces about 50 % muscle relaxant effect, and at 60 mg/kg dose all the treated animals showed muscle relaxation. Since strong muscle relaxation may seriously limit the therapeutic application of a drug, the lack of muscle relaxant effect of some novel compounds of the invention provides potential advantage over reference compound "A" in the clinical use.

Global ischemia induced by magnesium chloride

The experiments were carried out as described by Berga et al. /Berga, P., Beckett, P.R., Roberts, D.J., Llenas, J., Massingham, R.: Synergistic interactions between piracetam and dihydroergocristine in some animal models of cerebral hypoxia and ischemia, *Arzneim.-Forsch.*, 36, 1314-1320 (1986)/. Groups of 10 male NMRI mice weighing 20 to 25 g were

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treated ip. with the test substance in 10 mg/kg volume. After 30 minutes, saturated aqueous magnesium chloride solution was applied iv. (5 ml/kg) resulting in an immediate cardiac arrest. The elapsed time between the iv. injection and the last gasping was measured (gasping time). The means of the treated groups were expressed as percent of control.

Statistical analysis was done by ANOVA followed by DUNCAN test. The dose resulting in 50 % decrease in gasping time (ID_{50}) was calculated by linear regression. The results are shown in Table IV.

Table IV

Increase in gasping time in the magnesium chloride induced global ischemia test in mice

Compound (No. of Example)	Dose in mg/kg ip.	Effect in %	ID_{50} in mg/kg ip.
16	30	61	13
17	30	52	27
"A"	30	55	30

From Table IV it can be seen that the novel compound of Example 16 is as effective at neuroprotection in 13 mg/kg dose as the reference compound "A" in 30 mg/kg dose.

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Thus, the novel 8-substituted-9H-1,3-dioxolo/4,5-h//2,3/benzodiazepine derivatives of the formula I can be used as active ingredients of pharmaceutical compositions.

On the basis of the above test results, the novel compounds of the invention - due to their competitive AMPA/kainate antagonist property - have considerable muscle relaxant, neuroprotective and anticonvulsive effects. Consequently, the novel compounds can be used for the treatment of any disease such as epilepsy, diseases resulting in muscle spasm, neurodegenerative diseases, states after stroke, migraine and vomiting, wherein the inhibition of the AMPA/kainate receptors may have a favourable effect.

Some compounds of the invention which possess considerable anticonvulsive and neuroprotective activities, while they have no or weak muscle relaxant effect, can be primarily applied as antiepileptics. In the course of their application, the lack of muscle relaxant action provides notable benefit over the known AMPA/kainate antagonist 2,3-benzodiazepine derivatives.

The pharmaceutical compositions of the invention contain a therapeutically active amount of the compound of the formula I or a pharmaceutically suitable acid addition salt thereof and one or more conventional carrier(s).

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The pharmaceutical compositions of the invention are suitable for peroral, parenteral or rectal administration or for local treatment, and can be solid or liquid.

The solid pharmaceutical compositions suitable for peroral administration may be powders, capsules, tablets, film-coated tablets, microcapsules etc., and can comprise binding agents such as gelatine, sorbitol, poly(vinylpyrrolidone) etc.; filling agents such as lactose, glucose, starch, calcium phosphate etc.; auxiliary substances for tableting such as magnesium stearate, talc, poly(ethyleneglycol), silica etc.; wetting agents such as sodium laurylsulfate etc. as the carrier.

The liquid pharmaceutical compositions suitable for peroral administration may be solutions, suspensions or emulsions and can comprise e.g. suspending agents such as gelatine, carboxymethylcellulose etc.; emulsifiers such as sorbitane monooleate etc.; solvents such as water, oils, glycerol, propyleneglycol, ethanol etc.; preservatives such as methyl p-hydroxybenzoate etc. as the carrier.

Pharmaceutical compositions suitable for parenteral administration consist of sterile solutions of the active ingredient, in general.

Dosage forms listed above as well as other dosage forms are known per se, see e.g.

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group or a group of the formula $-NR^3R^4$,
wherein

R^3 and R^4 mean, independently, a hydrogen atom, a cyclopropyl group, a C_{1-4} alkoxy group, an amino group, a phenyl group optionally substituted by one or two methyl group(s) or a C_{1-4} alkyl group which latter is optionally substituted by a phenyl group or a saturated heterocyclic group having 5 or 6 members and comprising 1 to 3 nitrogen atom(s) or a nitrogen atom and an oxygen atom as the heteroatom, and the heterocyclic group is optionally substituted by a phenyl group which latter is optionally substituted by 1 to 3 methoxy groups,

or

R^3 and R^4 form, with the adjacent nitrogen atom and optionally with a further nitrogen atom or an oxygen atom, a saturated or unsaturated heterocyclic group having 5 or 6 members, being optionally substituted by a phenyl group that is optionally substituted by 1 to 3 methoxy groups, n has a value of 0, 1 or 2,

m has a value of 0, 1 or 2,

R^2 stands for a nitro group or an amino group, or a pharmaceutically suitable acid addition salt thereof as the active ingredient.

Within the above subgroup, the suitable pharmaceutical compositions of the invention

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contain a 1,3-dioxolo/4,5-h//2,3/benzodiazepine derivative of the formula I, wherein

R^3 and R^4 represent, independently, a hydrogen atom, a cyclopropyl group, a methoxy group, an amino group, a dimethylaminophenyl group or a C_{1-2} alkyl group which latter is substituted by a phenyl, morpholino or piperazinyl group, wherein the piperazinyl group is substituted by a methoxyphenyl group, or

R^3 and R^4 form, together with the adjacent nitrogen atom and optionally a further nitrogen atom or oxygen atom, an imidazolyl, morpholino or piperazinyl group, wherein the piperazinyl group is substituted by a methoxyphenyl group,

n has a value of 0 or 1,

m has a value of 0 or 1,

R^2 stands for a nitro group or an amino group,

A represents a hydrogen atom,

B means a hydrogen atom,

or a pharmaceutically suitable acid addition salt thereof as the active ingredient.

Within the above subgroup, the especially preferred pharmaceutical compositions of the invention contain a 1,3-dioxolo/4,5-h//2,3/-benzodiazepine derivative of the formula I, wherein

R^3 represents a hydrogen atom,

R^4 stands for a cyclopropyl group, a methoxy group or an amino group,

n has a value of 0,

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m has a value of 0,
R² means an amino group,
A represents a hydrogen atom,
B means a hydrogen atom,
or a pharmaceutically suitable acid addition
salt thereof as the active ingredient.

Another preferred subgroup of the
pharmaceutical compositions of the invention
contains an 8-methyl-7H-1,3-dioxolo[4,5-h/-
/2,3/benzodiazepine derivative of the formula
I, wherein

A forms together with B a valence bond
between the carbon atoms in positions
8 and 9,

R¹ represents a group of the formula

-CO-(CH₂)_p-R⁶, wherein

R⁶ stands for a halo atom, a phenoxy group,
a C₁₋₄ alkoxy group or a group of the
formula -NR⁷R⁸, wherein

R⁷ and R⁸ mean, independently, a hydrogen
atom, a guanlyl group or a C₁₋₄ alkyl
group which latter is optionally
substituted by a phenyl group or
a morpholino group, wherein the phenyl
group is optionally substituted by
one or two C₁₋₂ alkoxy group(s),
or

R⁷ and R⁸ form together with the adjacent
nitrogen atom an oxopyrrolidinyl
group, a phthalimido group or a
saturated heterocyclic group
having 5 or 6 members and comprising

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a hydrogen atom, a guanyl group or a C₁₋₃ alkyl group optionally substituted by a phenyl group, a dimethoxyphenyl group or a morpholino group, or

R⁷ and R⁸ form with the adjacent nitrogen atom an oxopyrrolidinyl group, a phthalimido group or a saturated heterocyclic group having 5 or 6 members and comprising one or two nitrogen atom(s) or a nitrogen and an oxygen atom as the heteroatom, and said heterocyclic group is optionally substituted by one or two identical or different substituent(s) selected from the group consisting of a hydroxy group, a methoxyphenyl group, a fluorophenyl group, a benzyl group or a (methoxyphenoxy)-(hydroxypropyl) group,

p has a value of 0, 1 or 2,

or a pharmaceutically suitable acid addition salt thereof as the active ingredient.

Within the latter subgroup, the especially preferred pharmaceutical compositions of the invention contain an 8-methyl-7H-1,3-dioxolo- /4,5-h//2,3/benzodiazepine derivative of the formula I, wherein

R² represents an amino group,

R¹, A and B are as defined above,

or a pharmaceutically suitable acid addition salt thereof as the active ingredient.

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Furthermore, the invention refers to a method of pharmaceutical treatment which comprises administering a therapeutically effective non-toxic amount of a 1,3-dioxolo-/4,5-h//2,3/benzodiazepine derivative of the formula I or a pharmaceutically suitable acid addition salt thereof to a patient suffering from especially epilepsy or a neurodegenerative disease or being in a state after stroke.

The invention is further elucidated, in detail, by means of the following Examples.

Example 1

(⁺)-7,8-Dihydro-8-methyl-5-(4-nitrophenyl)-9H-1,3-dioxolo/4,5-h//2,3/benzodiazepine-7-carboxylic acid-imidazolide

3.25 g (10.0 mmoles) of (⁺)-7,8-dihydro-8-methyl-5-(4-nitrophenyl)-9H-1,3-dioxolo-/4,5-h//2,3/benzodiazepine and 1.95 g (12.0 mmoles) of 1,1'-carbonyldiimidazole are boiled in 75 cm³ of anhydrous tetrahydrofuran for 20 hours. The reaction mixture is cooled with ice-water, the product precipitated is filtered, and washed with 50 cm³ of diethyl ether.

Thus, 3.58 g (85 %) of the title compound are obtained. M.p.: 244-248 °C.

¹H NMR (CDCl₃): δ 8.26 (2H, d, J=9.0 Hz), 7.91 (1H, s), 7.75 (2H, d, J=9.0 Hz), 7.31 (1H, s), 7.04 (1H, s), 6.88 (1H, s), 6.53 (1H, s), 6.08 (1H, d, J=1.3 Hz), 6.05 (1H,

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d, $J=1.3$ Hz), 5.24 (1H, m), 2.99 (1H, dd, $J=14.5$ and 4.8 Hz), 2.78 (1H, dd, $J=14.6$ and 10.2 Hz), 1.40 (3H, d, $J=6.4$ Hz).

Example 2

(⁺)-7,8-Dihydro-8-methyl-7-nicotinyl-5-(4-nitrophenyl)-9H-1,3-dioxolo[4,5-h//2,3/-benzodiazepine

3.25 g (10.0 mmoles) of (⁺)-7,8-dihydro-8-methyl-5-(4-nitrophenyl)-9H-1,3-dioxolo[4,5-h//2,3/-benzodiazepine are dissolved in 100 cm³ of anhydrous dichloromethane, to the solution obtained, 2.43 g (3.25 cm³, 24.0 mmoles) of triethylamine and, in small portions, 1.96 g (11.0 mmoles) of nicotinic acid hydrochloride are added. The reaction mixture is stirred at room temperature for 4 hours, then washed three times using 30 cm³ of water each time, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The crude product is crystallized from 70 cm³ of acetonitrile, and the crystals are washed with 15 cm³ of diethyl ether.

Thus, 3.40 g (79 %) of the title compound are obtained. M.p.: 226-228 °C.

¹H NMR (CDCl₃): δ 8.66 (2H, m), 8.14 (2H, d, $J=9.0$ Hz), 7.83 (1H, dt, $J=7.9$ and 2.0 Hz), 7.45 (2H, d, $J=9.0$ Hz), 7.37 (1H, m), 6.86 (1H, s), 6.51 (1H, s), 6.08 (1H, d, $J=1.3$ Hz), 6.06 (1H, d, $J=1.3$ Hz), 5.47 (1H, m),

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3.05 (1H, dd, J=14.4 and 4.2 Hz), 2.85 (1H, dd, J=14.4 and 9.6 Hz), 1.33 (3H, d, J=6.4 Hz).

Example 3

([±])-7,8-Dihydro-8-methyl-7-/N-(4-morpholinoethyl)carbamoyl/-5-(4-nitrophenyl)-9H-1,3-dioxolo/4,5-h//2,3/benzodiazepine

2.09 g (5.0 mmoles) of the imidazolidine derivative described in Example 1 are suspended in 100 cm³ of dichloromethane, and, to the suspension, 1.44 g (1.44 cm³, 11.0 mmoles) of (4-morpholinoethyl)amine are added. The reaction mixture is boiled for 10 hours, then washed three times using 30 cm³ of water each time, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The crude product is crystallized from 85 cm³ of acetonitrile, the crystals are washed with 10 cm³ of diethyl ether.

Thus, 1.83 g (76 %) of the title compound are obtained. M.p.: 198-203 °C.

¹H NMR (CDCl₃): δ 8.24 (2H, d, J=8.9 Hz), 7.68 (2H, d, J=8.9 Hz), 7.07 (1H, t, J=5.0 Hz), 6.73 (1H, s), 6.47 (1H, s), 6.01 (1H, s), 6.01 (1H, s), 6.00 (1H, s), 5.45 (1H, m), 3.71 (4H, m), 3.42 (2H, m), 3.12 (1H, dd, J=14.6 and 2.1 Hz), 2.87 (1H, dd, J=14.7 and 6.6 Hz), 2.55 (2H, m), 2.49 (4H, m), 0.97 (3H, d, J=6.6 Hz).

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Example 4

(\pm)-7-(N-Cyclopropylcarbamoyl)-7,8-dihydro-8-methyl-5-(4-nitrophenyl)-9H-1,3-dioxolo-
/4,5-h//2,3/benzodiazepine

2.09 g (5.0 mmoles) of the imidazolidine derivative described in Example 1 are boiled in 30 cm³ of cyclopropylamine for 4 hours, then the amine is distilled off under reduced pressure. The residue is taken up in 75 cm³ of dichloromethane, washed three times using 30 cm³ of water each time, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The crude product is crystallized from 50 cm³ of ethanol, and washed with 10 cm³ of diethyl ether.

Thus, 1.59 g (78 %) of the title compound are obtained. M.p.: 198-203 °C.

¹H NMR / (CD₃)₂SO/: δ 8.23 (2H, d, J=8.8 Hz), 7.77 (2H, d, J=8.1 Hz), 6.99 (1H, s), 6.85 (1H, d, J=2.8 Hz), 6.48 (1H, s), 6.07 (2H, s), 5.20 (1H, m), 3.00 (1H, dd, J=14.5 and 2.1 Hz), 2.86 (1H, dd, J=14.5 and 7.2 Hz), 2.60 (1H, m), 0.90 (3H, d, J=6.4 Hz), 0.63 (2H, m), 0.53 (2H, m).

Example 5

(\pm)-7,8-Dihydro-8-methyl-7-(N-methoxycarbamoyl)-5-(4-nitrophenyl)-9H-1,3-dioxolo-
/4,5-h//2,3/benzodiazepine

2.03 g (25.0 mmoles) of methoxyamine

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dichloromethane and 75 cm³ of water at room temperature for half an hour. The phases are separated, and the aqueous phase is extracted twice with 30 cm³ of dichloromethane each time. The combined organic phases are washed with 30 cm³ of water, and dried over anhydrous magnesium sulfate. To the thus-obtained solution, 2.09 g (5.0 mmoles) of the imidazolidine derivative described in Example 1 are added, the mixture is stirred at room temperature for 24 hours, then washed three times using 30 cm³ of water each time, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The crude product is crystallized from 55 cm³ of acetonitrile, and washed with 10 cm³ of diethyl ether.

Thus, 2.17 g (74 %) of the title compound are obtained. M.p.: 238-242 °C.

¹H NMR (CDCl₃): δ 8.22 (2H, d, J=8.8 Hz), 7.69 (2H, d, J=8.8 Hz), 7.19 (1H, t, J=4.8 Hz), 7.01 (3H, m), 6.91 (1H, m), 6.73 (1H, s), 6.46 (1H, s), 5.99 (1H, s), 5.98 (1H, s), 5.45 (1H, m), 3.87 (3H, s), 3.46 (2H, m), 3.10 (5H, m), 2.85 (1H, dd, J=14.8 and 6.4 Hz), 2.70 (4H, m), 2.63 (2H, m), 0.98 (3H, d, J=6.6 Hz).

Example 7

(⁺)-7-(N-Aminocarbamoyl)-7,8-dihydro-8-methyl-5-(4-nitrophenyl)-9H-1,3-dioxolo[4,5-h]/2,3-benzodiazepine

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2.09 g (5.0 mmoles) of the imidazolidine derivative described in Example 1 are suspended in 75 cm³ of dichloromethane. To the suspension, 1.25 g (1.21 cm³, 25.0 mmoles) of 98-100 % hydrazine hydrate are added. The reaction mixture is stirred at room temperature for 10 hours, then washed three times using 30 cm³ of water each time, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The crude product is crystallized from 45 cm³ of ethanol, and the crystals are washed with 10 cm³ of diethyl ether.

Thus, 1.04 g (54 %) of the title compound are obtained. M.p.: 219-220 °C.

¹H NMR (CDCl₃): δ 8.23 (2H, d, J=9.0 Hz), 7.62 (2H, d, J=9.0 Hz), 7.52 (1H, broad s), 6.73 (1H, s), 6.45 (1H, s), 6.01 (1H, d, J=1.3 Hz), 6.00 (1H, d, J=1.3 Hz), 5.38 (1H, m), 3.82 (2H, broad s), 3.12 (1H, dd, J=14.8 and 2.0 Hz), 2.86 (1H, dd, J=14.8 and 6.5 Hz), 0.99 (3H, d, J=6.6 Hz).

Example 8

([±])-2-/-7,8-Dihydro-8-methyl-5-(4-nitrophenyl)-9H-1,3-dioxolo[4,5-h//2,3/benzodiazepine-7-yl/-N-(2,6-dimethylphenyl)acetamide

A mixture of 9.80 g (30.0 mmoles) of ([±])-7,8-Dihydro-8-methyl-5-(4-nitrophenyl)-9H-1,3-dioxolo[4,5-h//2,3/benzodiazepine and 7.10 g (36.0 mmoles) of 2-chloro-N-(2,6-dimethylphenyl)acetamide is heated at 140

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°C for 2 hours, then at 160 °C again for 2 hours. The reaction mixture is cooled back and dissolved in 200 cm³ of chloroform. The organic phase is washed with 50 cm³ of 10 % aqueous sodium hydroxide and 100 cm³ of water, dried over anhydrous magnesium sulfate, and evaporated. The evaporation residue is subjected to chromatography over silica gel (Kieselgel G, 0.2-0.063 mm) using a mixture of hexane and acetone as the eluent.

Thus, 4.38 g (30 %) of the title compound are obtained. M.p.: 172-174 °C.

¹H NMR (CDCl₃): δ 8.22 (2H, d, J=9.1 Hz), 7.82 (2H, d, J=9.1 Hz), 7.65 (1H, s), 7.03 (3H, s), 6.86 (1H, s), 6.45 (1H, s), 6.02 (2H, bs), 4.15 (1H, d, J=16.8 Hz), 4.05 (1H, m), 3.96 (1H, d, J=16.8 Hz), 2.96 (1H, dd, J=14.0 Hz, J= 5.8 Hz), 2.48 (1H, dd, J=14.0 Hz, J=4.3 Hz), 2.07 (6H, s), 1.3 (3H, d, J=6.2 Hz).

Example 9

(⁺)-2-/-7,8-Dihydro-8-methyl-5-(4-nitrophenyl)-9H-1,3-dioxolo/4,5-h//2,3/benzodiazepine-7-yl/acetamide

9.80 g (30.0 mmoles) of (⁺)-7,8-dihydro-8-methyl-5-(4-nitrophenyl)-9H-1,3-dioxolo/4,5-h//2,3/benzodiazepine and 3.40 g (36 mmoles) of 2-chloroacetamide are heated at 160 °C for 6 hours. The reaction mixture is cooled back, and dissolved in 200 cm³ of

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chloroform. The organic phase is washed with 50 cm³ of 10 % aqueous sodium hydroxide and 100 cm³ of water, dried over anhydrous magnesium sulfate, and evaporated. The evaporation residue is subjected to chromatography over silica gel (Kieselgel G, 0.2-0.063 mm) using a mixture of hexane and acetone as the eluent.

Thus, 3.30 g (29 %) of the title compound are obtained. M.p.: 216-218 °C.

¹H NMR (CDCl₃): δ 8.20 (2H, d, J=9.1 Hz), 7.66 (2H, d, J=9.1 Hz), 7.07 (1H, s), 6.97 (1H, s), 6.87 (1H, s), 6.54 (1H, s), 6.06 (2H, s), 4.10 (1H, m), 3.91 (1H, d, J=16.8 Hz), 3.79 (1H, d, J=16.8 Hz), 3.05 (1H, dd, J=14.0 Hz, J=3.4 Hz), 2.59 (1H, dd, J=14.0 Hz, J=5.2 Hz), 0.97 (3H, d, J=6.2 Hz).

Example 10

(⁺)-7,8-Dihydro-7-(2-chloroacetyl)-8-methyl-5-(4-nitrophenyl)-9H-1,3-dioxolo[4,5-h//2,3/-]benzodiazepine

9.80 g (30.0 mmoles) of (⁺)-7,8-Dihydro-8-methyl-5-(4-nitrophenyl)-9H-1,3-dioxolo[4,5-h//2,3/-]benzodiazepine are boiled with 20 cm³ of 2-chloroacetyl chloride for 30 minutes, then the reaction mixture is evaporated, and the residue is suspended in 100 cm³ of diethyl ether. The crystals obtained are filtered, and washed with 20 cm³ of diethyl ether.

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Thus, 11.22 g (93 %) of the title compound are obtained. M.p.: 220-222 °C.

¹H NMR (CDCl₃): δ 8.27 (2H, d, J=9.0 Hz), 7.73 (2H, d, J=9.0 Hz), 6.77 (1H, s), 6.47 (1H, s), 6.03 (2H, s), 5.35 (1H, m), 4.57 (1H, d, J=13.8 Hz), 4.47 (1H, d, J=13.8 Hz), 3.08 (1H, dd, J=14.6 Hz, J=3.2 Hz), 2.82 (1H, dd, J=14.6 Hz, J=8.0 Hz), 1.06 (3H, d, J=6.6 Hz).

Example 11

([±])-7,8-Dihydro-8-methyl-7-[3-/4-(2-methoxyphenyl)piperazinyl/propionyl]-5-(4-nitrophenyl)-9H-1,3-dioxolo/4,5-h//2,3/benzodiazepine

A mixture of 6.40 g (16.0 mmoles) of ([±])-7,8-dihydro-7-(2-chloroacetyl)-8-methyl-5-(4-nitrophenyl)-9H-1,3-dioxolo/4,5-h//2,3/benzodiazepine, 7.68 g (40.0 mmoles) of 4-(2-methoxyphenyl)piperazine and 32 cm³ of acetonitrile is boiled for 30 minutes. Then, the reaction mixture is evaporated. To the evaporation residue, 50 cm³ of water are added, the crystals obtained are filtered, and washed with 10 cm³ of water.

Thus, 7.90 g (89 %) of the title compound are obtained. M.p.: 175-176 °C.

Example 12

([±])-7,8-Dihydro-8-methyl-7-morpholinoacetyl-5-(4-nitrophenyl)-9H-1,3-dioxolo/4,5-h//2,3/benzodiazepine

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A mixture of 6.00 g (15.0 mmoles) of (+)-7,8-dihydro-7-(2-chloroacetyl)-8-methyl-5-(4-nitrophenyl)-9H-1,3-dioxolo[4,5-h]/2,3/benzodiazepine, 3.00 g (36.0 mmoles) of morpholine and 30 cm³ of acetonitrile is boiled for 2 hours. Then, the reaction mixture is evaporated. To the evaporation residue, 100 cm³ of diethyl ether are added, the crystals obtained are filtered, and recrystallized from a mixture of 2-propanol and water.

Thus, 4.90 g (73 %) of the title compound are obtained. M.p. 206-208 °C.

Example 13

(+)-7-[2-/N-Benzyl-N-(2-morpholinoethyl)-amino/acetyl]-7,8-dihydro-8-methyl-5-(4-nitrophenyl)-9H-1,3-dioxolo[4,5-h]/2,3-benzodiazepine

A mixture of 4.00 g (10.0 mmoles) of (+)-7,8-dihydro-7-(2-chloroacetyl)-8-methyl-5-(4-nitrophenyl)-9H-1,3-dioxolo[4,5-h]/2,3/benzodiazepine, 5.50 g (25.0 mmoles) of N-benzyl-N-(2-morpholinoethyl)amine and 20 cm³ of acetonitrile is boiled for 1 hour. Then, the reaction mixture is evaporated. To the evaporation residue, 50 cm³ of diethyl ether are added, and the crystals obtained are filtered. The mother liquor is evaporated, and the evaporation residue is subjected to chromatography over silica gel (Kieselgel

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G, 0.2-0.063 mm) using a mixture of chloroform and methanol as the eluent.

Thus, 5.10 g (87 %) of the title compound are obtained as an oil.

^1H NMR (CDCl_3): δ 8.22 (2H, d, $J=9.0$ Hz), 7.61 (2H, d, $J=9.0$ Hz), 7.3 (5H, m), 6.75 (1H, s), 6.44 (1H, s), 6.02 (2H, s), 5.40 (1H, m), 3.93 (1H, d, $J=17.5$ Hz), 3.92 (2H, s), 3.77 (1H, d, $J=17.5$ Hz), 3.66 (4H, t, $J=4.7$ Hz), 3.04 (1H, dd, $J=14.6$ Hz, $J=2.9$ Hz), 2.92 (2H, t, $J=7.1$ Hz), 2.78 (1H, dd, $J=14.6$ Hz, $J=11.8$ Hz), 2.49 (2H, t, $J=7.1$ Hz), 2.39 (4H, t, $J=4.7$ Hz), 1.06 (3H, d, $J=6.6$ Hz).

Examples 14 to 19

A general process for reducing the nitro group of the compounds described in Examples 2 to 7 by catalytical hydrogenation

5.0 mmoles of the nitro compound are dissolved in a mixture of 100 cm^3 of dichloromethane and 100 cm^3 of methanol, and the solution is hydrogenized in the presence of 0.10 g of 10 % palladium/carbon catalyst at room temperature and 5.065×10^5 Pa pressure. Following the hydrogenization, the catalyst is filtered, the solvent is evaporated under reduced pressure, and the crude product is recrystallized. The following compounds are obtained:

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Example 14

(⁺)-5-(4-Aminophenyl)-7,8-dihydro-8-methyl-7-nicotinyl-9H-1,3-dioxolo[4,5-h//2,3/-benzodiazepine

Solvent for crystallization: toluene.

M.p.: 221-223 °C.

Yield: 61 %.

Analysis: for C₂₃H₂₀N₄O₃ (400.44)

calculated: C 68.99 %, H 5.03 %, N 13.99 %;

found: C 69.53 %, H 5.16 %, N 13.56 %.

¹H NMR /CDCl₃ + (CD₃)₂SO, 70 °C/: δ 8.54 (1H, dd, J=4.8 and 1.5 Hz), 8.49 (1H, m), 7.65 (1H, m), 7.31 (1H, dd, J=7.8 and 4.8 Hz), 7.11 (2H, d, J=8.5 Hz), 6.70 (1H, s), 6.57 (1H, s), 6.53 (2H, d, J=8.5 Hz), 6.03 (1H, s), 6.01 (1H, s), 5.21 (1H, m), 5.09 (2H, s), 2.81 (1H, dd, J=13.9 and 5.6 Hz), 2.63 (1H, t, J=13.5 Hz), 1.37 (3H, d, J=6.0 Hz).

Example 15

(⁺)-5-(4-Aminophenyl)-7,8-dihydro-8-methyl-7-/N-(4-morpholinoethyl)carbamoyl/-9H-1,3-dioxolo[4,5-h//2,3/- benzodiazepine

Solvent for crystallization: dichloromethane.

M.p.: 262-264 °C.

Yield: 66 %.

Analysis: for C₂₄H₂₉N₅O₄ (451.53)

calculated: C 63.84 %, H 6.47 %, N 15.51 %;

found: C 63.96 %, H 6.41 %, N 15.30 %.

¹H NMR /(CD₃)₂SO/: δ 7.41 (2H, d, J=8.6 Hz),

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6.98 (1H, s), 6.65 (2H, d, J=8.6 Hz), 6.54 (1H, s), 6.40 (1H, t, J=5.3 Hz), 6.06 (1H, s), 6.03 (1H, s), 5.50 (2H, broad s), 4.87 (1H, m), 3.64 (4H, m), 3.22 (2H, m), 2.83 (1H, dd, J=13.8 and 5.2 Hz), 2.42 (7H, m), 1.10 (3H, d, J=6.2 Hz).

Example 16

(⁺)-5-(4-Aminophenyl)-7-(N-cyclopropyl-carbamoyl)-7,8-dihydro-8-methyl-9H-1,3-dioxolo[4,5-h//2,3]benzodiazepine

Solvent for crystallization: ethanol.

M.p.: 158-160 °C.

Yield: 72 %.

Analysis: for C₂₁H₂₂N₄O₃ (378.43)

calculated: C 66.65 %, H 5.85 %, N 14.80 %;

found: C 65.96 %, H 6.09 %, N 14.52 %.

¹H NMR / (CD₃)₂SO/: δ 7.38 (2H, d, J=8.4 Hz), 6.98 (1H, s), 6.57 (2H, d, J=8.4 Hz), 6.53 (1H, s), 6.13 (1H, d, J=3.0 Hz), 6.06 (1H, s), 6.02 (1H, s), 5.68 (2H, broad s), 4.80 (1H, m), 2.78 (1H, dd, J=13.5 and 5.6 Hz), 2.50 (1H, m), 2.35 (1H, t, J=12.7 Hz), 1.07 (3H, d, J=6.1 Hz), 0.55 (2H, m), 0.45 (2H, m).

Example 17

(⁺)-5-(4-Aminophenyl)-7,8-dihydro-8-methyl-7-(N-methoxycarbamoyl)-9H-1,3-dioxolo[4,5-h//2,3]benzodiazepine

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Solvent for crystallization: ethanol.

M.p.: 159-162 °C.

Yield: 75 %.

Analysis: for $C_{19}H_{20}N_4O_4$ (368.40)

calculated: C 61.95 %, H 5.47 %, N 15.21 %;

found: C 61.62 %, H 5.56 %, N 15.32 %.

1H NMR ($CDCl_3$): δ 9.23 (1H, s), 7.46 (2H, d, J=8.7 Hz), 6.99 (1H, s), 6.56 (2H, d, J=8.7 Hz), 6.53 (1H, s), 6.07 (1H, d, J=1.0 Hz), 6.03 (1H, d, J=1.0 Hz), 5.68 (2H, broad s), 4.75 (1H, m), 3.53 (3H, s), 2.79 (1H, dd, J=13.7 and 5.7 Hz), 2.36 (1H, dd, J=13.5 and 12.0 Hz), 1.12 (3H, d, J=6.1 Hz).

Example 18

(\pm)-5-(4-Aminophenyl)-7,8-dihydro-8-methyl-7-[N-/1-(2-methoxyphenyl)-4-piperazinyl-ethyl/carbamoyl]-9H-1,3-dioxolo[4,5-h/-/2,3/benzodiazepine

Solvent for crystallization: diethyl ether.

M.p.: 121-130 °C.

Yield: 81 %.

Analysis: for $C_{31}H_{36}N_6O_4$ (556.67)

calculated: C 66.89 %, H 6.52 %, N 15.11 %;

found: C 66.52 %, H 6.68 %, N 15.02 %.

1H NMR ($CDCl_3$): δ 7.46 (2H, d, J=8.4 Hz), 6.96 (3H, m), 6.88 (1H, d, J=8.0 Hz), 6.73 (1H, s), 6.67 (1H, t, J=4.8 Hz), 6.60 (2H, d, J=8.4 Hz), 6.59 (1H, s), 5.95 (1H, d, J=1.3 Hz), 5.93 (1H, d, J=1.3 Hz), 5.16 (1H, m), 3.87 (5H, broad s), 3.44 (1H, m), 3.37 (1H,

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m), 3.16 (4H, m), 2.84 (1H, dd, J=14.0 and 4.4 Hz), 2.70 (4H, m), 2.65 (1H, dd, J=14.0 and 10.0 Hz), 2.58 (2H, m), 1.17 (3H, d, J=6.4 Hz).

Example 19

(⁺)-5-(4-Aminophenyl)-7-(N-aminocarbamoyl)-7,8-dihydro-8-methyl-9H-1,3-dioxolo[4,5-h]/2,3/benzodiazepine

Solvent for crystallization: acetonitrile.

M.p.: 160-170 °C.

Yield: 64 %.

Analysis: for C₁₈H₁₉N₅O₃ (353.38)

calculated: C 61.18 %, H 5.42 %, N 19.82 %;

found: C 59.68 %, H 5.37 %, N 19.32 %.

¹H NMR (CDCl₃): δ 7.42 (2H, d, J=8.6 Hz), 7.07 (1H, s), 6.99 (1H, s), 6.56 (2H, d, J=8.6 Hz), 6.53 (1H, s), 6.07 (1H, d, J=0.8 Hz), 6.03 (1H, d, J=0.8 Hz), 5.68 (2H, s), 4.78 (1H, m), 3.96 (2H, s), 2.78 (1H, dd, J=13.7 and 5.7 Hz), 2.37 (1H, t, J=12.2 Hz), 1.11 (3H, d, J=6.2 Hz).

Example 20

(⁺)-2-/5-(4-Aminophenyl)-7,8-dihydro-8-methyl-1,3-dioxolo[4,5-h]/2,3/benzodiazepine-7-yl/-N-(2,6-dimethylphenyl)acetamide

2.20 g (4.5 mmoles) of (⁺)-2-/7,8-dihydro-8-methyl-5-(4-nitrophenyl)-1,3-dioxolo[4,5-h]/2,3/benzodiazepine-7-yl/-N-(2,6-

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-dimethylphenyl)acetamide are dissolved in 22 cm³ of ethanol, to the solution obtained, 0.22 g 10 % palladium/carbon catalyst suspended in 0.5 cm³ of water are added. To the reaction mixture, a solution of 1.80 g (21.4 mmoles) of potassium formate in 1.8 cm³ of water is added, drop by drop. The reaction mixture is stirred at room temperature for 4 hours, then the catalyst is filtered, the solvent is evaporated under reduced pressure, and the crude product is recrystallized from 2-propanol.

Thus, 0.90 g (44 %) of the title compound are obtained. M.p.: 219-221 °C.

Analysis: for C₂₇H₂₈N₄O₅ (456.55)

calculated: N 12.33 %;

found: N 11.85 %.

¹H NMR (DMSO-d₆): δ 8.01 (1H, s), 7.26 (2H, d, J=8.5 Hz), 7.0 (4H, m), 6.54 (2H, d, J=8.5 Hz), 6.46 (1H, s), 6.02 (2H, s), 5.52 (2H, s), 3.80 (1H, m), 3.76 (1H, d, J=15.6 Hz), 3.64 (1H, d, J=15.6 Hz), 2.78 (1H, dd, J=13.2 Hz, J=6.2 Hz), 2.35 (1H, dd, J=13.2 Hz, J=5.8 Hz), 1.96 (6H, s), 1.16 (3H, d, J=6.1 Hz).

Example 21

([±])-2-/5-(4-Aminophenyl)-7,8-dihydro-8-methyl-1,3-dioxolo[4,5-h]/2,3/benzodiazepine-7-yl/-acetamide

A mixture of 1.52 g (4.0 mmoles) of ([±])-2-/7,8-dihydro-8-methyl-5-(4-nitrophenyl)-

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-1,3-dioxolo/4,5-h//2,3/benzodiazepine-7-yl/-acetamide, 3.60 g (16.0 mmoles) of tin(II) chloride dihydrate and 60 cm³ of methanol is boiled for 8 hours, then, further 1.00 g (4.4 mmoles) of tin(II) chloride dihydrate are added to the reaction mixture, and boiling is continued for another 2 hours. The reaction mixture is evaporated, and, to the evaporation residue, 40 cm³ of water and 40 cm³ of chloroform are added. The aqueous phase is extracted still twice with 40 cm³ of chloroform each time. To the aqueous phase, a solution of 4 g of sodium hydroxide in 20 cm³ of water are added, and the mixture is extracted twice using 40 cm³ of chloroform each time. The organic phase is washed twice with 30 cm³ of water each time, dried over anhydrous magnesium sulfate, and evaporated. The evaporation residue is subjected to chromatography over silica gel (Kieselgel G, 0.2-0.063) using a mixture of hexane and acetone as the eluent.

Thus, 0.95 g (68 %) of the title compound are obtained. M.p.: 221-223 °C.

¹H NMR (DMSO-d₆): δ 7.22 (2H, d, J=8.7 Hz), 6.99 (1H, s), 6.95 (1H, d, J=3.6 Hz), 6.54 (1H, s), 6.53 (2H, d, J=8.7 Hz), 6.04 (2H, s), 5.94 (1H, d, J=3.6 Hz), 5.48 (2H, s), 3.66 (1H, m), 3.48 (1H, d, J=16.2 Hz), 3.41 (1H, d, J=16.2 Hz), 2.70 (1H, dd, J=5.7, J=13.5 Hz), 2.30 (1H, dd, J=5.7 Hz, J=13.5 Hz), 1.07 (3H, d, J=6.1 Hz).

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Example 22

(⁺)-2-/5-(4-Aminophenyl)-7,8-dihydro-8-methyl-
-7-[3-/4-(2-methoxyphenyl)piperazinyl/-
propionyl]-1,3-dioxolo/4,5-h//2,3/-
benzodiazepine-7-yl/-acetamide

A mixture of 8.36 g (15.0 mmoles) of
(⁺)-2-/7,8-dihydro-8-methyl-7-[3-/4-(2-
-methoxyphenyl)piperazinyl/propionyl]-5-
-(4-nitrophenyl)-1,3-dioxolo/4,5-h//2,3/-
benzodiazepine, 20.40 g (90.0 mmoles) of
tin(II) chloride dihydrate and 150 cm³ of
methanol is boiled for 1 hour. The reaction
mixture is evaporated, and, to the evaporation
residue, 200 cm³ of water and 100 cm³ of
chloroform are added. The aqueous phase is
extracted still twice with 100 cm³ of
chloroform each time. Then, to the aqueous
phase, a solution of 25 g of sodium hydroxide
in 150 cm³ of water are added, and the aqueous
phase is extracted three times using 150 cm³
of chloroform each time. The organic phase
is washed twice with 150 cm³ of water each
time, dried over anhydrous magnesium sulfate,
and evaporated. The evaporation residue is
subjected to chromatography over silica gel
(Kieselgel G, 0.2-0.063 mm) using a mixture
of chloroform and methanol as the eluent.

Thus, 4.36 g (55 %) of the title compound
are obtained. M.p.: 253-254 °C.

Analysis: for C₃₀H₃₃N₅O₄ (527.63)

calculated: C 68.29 %, H 6.30 %, N 13.27 %;

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found: C 57.89 %, H 6.27 %, N 13.31 %.
 ^1H NMR (CDCl_3): δ 7.51 (2H, d, $J=8.7$ Hz),
 6.92 (4H, m), 6.76 (1H, s), 6.68 (2H, d, $J=8.7$
 Hz), 6.60 (1H, s), 6.00 (1H, s), 5.95 (1H,
 s), 5.22 (1H, m), 4.1 (2H, s), 3.84 (3H, s),
 3.45 (1H, m), 3.15 (1H, d, $J=15.6$ Hz), 3.08
 (4H, m), 2.65 (6H, m), 1.32 (3H, d, $J=6.4$
 Hz).

Example 23

($^+$)-5-(4-Aminophenyl)-7,8-dihydro-8-methyl-
 -7-[3-/4-(2-methoxyphenyl)piperazinyl/-
 propionyl]-1,3-dioxolo[4,5-h//2,3/-
 benzodiazepine difumarate dihydrate

1.63 g (3.0 mmoles) of ($^+$)-5-(4-amino-
 phenyl)-7,8-dihydro-8-methyl-7-[3-/4-(2-
 -methoxyphenyl)piperazinyl/propionyl]-1,3-
 dioxolo[4,5-h//2,3/benzodiazepine and 0.7
 g (6 mmoles) of fumaric acid are boiled in
 a mixture of 60 cm^3 of ethanol and 90 cm^3
 of dichloromethane for 30 minutes. The hot
 reaction mixture is filtered, evaporated,
 and the residue is suspended in 50 cm^3 of
 diethyl ether. The crystals are filtered.

Thus, 1.75 g (73 %) of the title compound
 are obtained. M.p.: 162-164 $^{\circ}\text{C}$.

Analysis: for $\text{C}_{38}\text{H}_{45}\text{N}_5\text{O}_{14}$ (795.81)

calculated: C 57.35 %, H 5.70 %, N 8.80 %;

found: C 57.25 %, H 5.67 %, N 8.84 %.

^1H NMR ($\text{DMSO}-d_6$): δ 7.38 (2H, d, $J=8.7$ Hz),
 7.01 (1H, s), 6.92 (2H, m), 6.84 (2H, m),

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6.62 (7H, m), 6.07 (1H, s), 6.06 (1H, s),
4.95 (1H, m), 3.75 (3H, s), 3.34 (1H, d, J=13.5
Hz), 3.22 (1H, d, J=13.5 Hz), 2.90 (4H, m),
2.80 (1H, dd, J=5.3 Hz, J=13.6 Hz), 2.63 (4H,
m), 2.47 (1H, m), 1.18 (3H, d, J=6.2 Hz).

Example 24

(⁺)-5-(4-Aminophenyl)-7,8-dihydro-8-methyl-
-7-morpholinoacetyl-9H-1,3-dioxolo[4,5-h//2,3/-
benzodiazepine

5.00 g (11.0 mmoles) of (⁺)-7,8-Dihydro-
-8-methyl-7-morpholinoacetyl-5-(4-nitrophenyl)-
-9H-1,3-dioxolo[4,5-h//2,3/benzodiazepine
are dissolved in 50 cm³ of ethanol. To the
solution, 0.50 g of 10 % palladium/carbon
catalyst suspended in 1.0 cm³ of water are
added. Then, to the reaction mixture, a
solution of 4.00 g (47.6 mmoles) of potassium
formate in 4.0 cm³ of water are added, drop
by drop. The reaction mixture is stirred at
room temperature for 2 hours, then again a
solution of 2.00 g (23.8 mmoles) of potassium
formate in 2.0 cm³ of water are added, drop
by drop. After further 2 hours' stirring,
the catalyst is filtered, washed with a large
quantity of ethanol, the solvent is evaporated
under reduced pressure, and the residue is
suspended in 100 cm³ of diethyl ether. The
crystals obtained are filtered, and the crude
product is recrystallized from a mixture of
acetonitrile and water.

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Thus, 3.00 g (65 %) of the title compound are obtained. M.p.: 254-256 °C.

Analysis: for $C_{23}H_{26}N_4O_4$ (422.49)

calculated: N 13.26 %, H 6.20 %;

found: N 13.12 %, H 6.48 %.

1H NMR ($CDCl_3$): δ 7.49 (2H, d, $J=8.6$ Hz), 6.75 (1H, s), 6.68 (2H, d, $J=8.6$ Hz), 6.58 (1H, s), 6.00 (1H, s), 5.97 (1H, s), 5.19 (1H, m), 4.1 (2H, bs), 3.69 (4H, t, $J=4.6$ Hz), 3.36 (1H, d, $J=15.8$ Hz), 3.07 (1H, d, $J=15.8$ Hz), 2.64 (2H, m), 2.53 (4H, m), 1.30 (3H, d, $J=6.4$ Hz).

Example 25

(+)-5-(4-Aminophenyl)-7-[2-/N-benzyl-N-(2-morpholinoethyl)amino/acetyl]-7,8-dihydro-8-methyl-9H-1,3-dioxolo[4,5h][2,3]-benzodiazepine

5.10 g (8.7 mmoles) of 7-[2-/N-benzyl-N-(2-morpholinoethyl)amino/acetyl]-7,8-dihydro-8-methyl-5-(4-nitrophenyl)-9H-1,3-dioxolo[4,5h][2,3]-benzodiazepine are dissolved in 120 cm³ of methanol. To the solution, 1.30 g of 10 % palladium/carbon catalyst suspended in 11 cm³ of water are added, and, to the reaction mixture, 7.70 cm³ (15.8 mmoles) of hydrazine hydrate are added, drop by drop. The reaction mixture is stirred at room temperature for 24 hours, then further 2.00 cm³ (4.1 mmoles) of hydrazine hydrate are added. After further 48 hours' stirring, the

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catalyst is filtered, washed with a large quantity of methanol, the solvent is evaporated under reduced pressure, and the residue is subjected to chromatography over silica gel (Kieselgel G, 0.2-0.063 mm) using a mixture of acetone and hexane as the eluent.

Thus, 3.70 g (77 %) of the title compound are obtained. M.p.: 68-70 °C.

Analysis: for $C_{32}H_{37}N_5O_4$ (555.683)

calculated: N 12.60 %, H 6.71 %;

found: N 12.16 %, H 6.93 %.

1H NMR ($CDCl_3$): δ 7.43 (2H, d, $J=8.7$ Hz), 7.25 (5H, m), 6.76 (1H, s), 6.64 (2H, d, $J=8.7$ Hz), 6.51 (1H, s), 6.01 (1H, s), 5.97 (1H, s), 5.20 (1H, m), 3.99 (2H, bs), 3.84 (2H, s), 3.68 (1H, d, $J=16.8$ Hz), 3.63 (4H, t, $J=4.6$ Hz), 3.25 (1H, d, $J=16.8$ Hz), 2.82 (2H, m), 2.65 (2H, m), 2.43 (2H, m), 2.36 (4H, m), 1.26 (3H, d, $J=6.2$ Hz).

Example 26

Phenyl 8-methyl-5-(4-nitrophenyl)-7H-1,3-dioxolo[4,5-h//2,3]benzodiazepine-7-carboxylate

20.0 g (61.9 mmoles) of 8-methyl-5-(4-nitrophenyl)-7H-1,3-dioxolo[4,5-h//2,3]-benzodiazepine are added to 600 cm³ of chloroform, and, to the mixture, 37.2 g (237.6 mmoles) of phenyl chloroformate are added, drop by drop, at 5 to 10 °C in 15 minutes. The suspension is boiled for 7 hours, while

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the mixture becomes a clear solution. After cooling, the solution is evaporated under reduced pressure, to the evaporation residue, 300 cm³ of diethyl ether are added, and the mixture is stirred at 25 °C for 16 hours. The crystals obtained are filtered, and washed three times using 50 cm³ of diethyl ether each time.

Thus, 26.0 g (94.9 %) of the title compound are obtained. M.p.: 218-220 °C.
¹H NMR (CDCl₃): δ 8.25 (2H, d, J=9.0 Hz), 7.77 (2H, d, J=9.0 Hz), 7.4 (2H, m), 7.2 (3H, m), 6.81 (1H, s), 6.55 (1H, s), 6.07 (1H, s), 6.02 (1H, s), 6.36 (1H, qa, J=1.1 Hz), 2.36 (3H, d, J=1.1 Hz).

Example 27

7-(2-Chloroacetyl)-8-methyl-5-(4-nitrophenyl)-7H-1,3-dioxolo[4,5-h]/2,3/benzodiazepine

To 45 cm³ (564.6 mmoles) of chloroacetyl chloride, 15.0 g (46.4 mmoles) of 8-methyl-5-(4-nitrophenyl)-7H-1,3-dioxolo[4,5-h]/2,3/benzodiazepine are added under ice-water cooling in 10 minutes. After 5 minutes' stirring at 25 °C, the solution becomes cloudy. The mixture is stirred at 80 °C for 60 minutes, then boiled for 15 minutes. After cooling, the mixture is poured onto 450 g of ice, stirred for 3 hours, the crystals precipitated are filtered, washed three times using 60 cm³ of water each time, and dried under a

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lamp emitting infra red radiation. The crude product is boiled in 150 cm³ of ethanol for 5 minutes. After cooling, the crystals are filtered, washed with ethanol and diethyl ether.

Thus, 15.5 g (83.5 %) of the title compound are obtained. M.p.: 228-229 °C.

Analysis: for C₁₉H₁₄ClN₃O₅ (399.79)

calculated: N 10.51 %;

found: N 10.28 %.

¹H NMR (CDCl₃): δ 8.28 (2H, d, J=8.8 Hz), 7.71 (2H, d, J=8.8 Hz), 6.77 (1H, s), 6.48 (1H, s), 6.38 (1H, bs), 6.05 (2H, s), 4.09 (2H, s), 2.28 (3H, s).

Example 28

7-(3-Chloropropionyl)-8-methyl-5-(4-nitrophenyl)-7H-1,3-dioxolo/4,5-h//2,3/-benzodiazepine

To 45 cm³ (461.9 mmoles) of 3-chloropropionyl chloride, 15.0 g (46.4 mmoles) of 8-methyl-5-(4-nitrophenyl)-7H-1,3-dioxolo/4,5-h//2,3/-benzodiazepine are added under ice-water cooling in 10 minutes. The mixture is stirred at 25 °C for 22 hours, then poured onto 450 g of ice. After 3 hours' stirring, the crystals precipitated are filtered, washed three times with 60 cm³ of water each time, and dried under a lamp emitting infra red radiation. The crude product is dissolved in 300 cm³ of dichloromethane, and washed

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with 200 cm³ of water. The organic phase is evaporated under reduced pressure, and the evaporation residue is boiled in 100 cm³ of ethanol for 10 minutes. After cooling, the crystals are filtered, washed with ethanol and diethyl ether.

Thus, 14.1 g (73.4 %) of the title compound are obtained. M.p.: 207-209 °C.

Analysis: for C₂₀H₁₆ClN₃O₅ (413.82)
calculated: C 58.05 %, H 3.90 %, N 10.15 %, Cl 8.57 %;

found: C 58.66 %, H 4.02 %, N 9.96 %, Cl 8.53 %.

¹H NMR (CDCl₃): δ 8.28 (2H, d, J=8.8 Hz), 7.71 (2H, d, J=8.8 Hz), 6.77 (1H, s), 6.48 (1H, s), 6.35 (1H, bs), 6.05 (2H, bs), 3.86 (2H, m), 3.1-2.9 (2H, m), 2.27 (3H, s).

Example 29

8-Methyl-7-methylcarbamoyl-5-(4-nitrophenyl)-7H-1,3-dioxolo-/4,5-h//2,3/benzodiazepine

5 g (11.3 mmoles) of the compound prepared according to Example 26, 50 cm³ of ethanol and 14.4 cm³ (136.6 mmoles) of 33 % methylamine in ethanol are transferred to an acid resistant steel bomb tube of 200 cm³ capacity. The bomb tube is sealed, and the mixture is stirred at 90 °C for 8 hours. The mixture is allowed to stand at 25 °C for a night, on the other day the bomb tube is opened. The crystals precipitated are filtered, washed three times

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using 5 cm³ of ethanol each time, then twice with 20 cm³ of diethyl ether each time.

Thus, 3.6 g (83.9 %) of the title compound are obtained. M.p.: higher than 250 °C.

¹H NMR (CDCl₃): δ 8.25 (2H, d, J=8.8 Hz), 7.67 (2H, d, J=8.8 Hz), 6.70 (1H, s), 6.40 (1H, s), 6.15 (1H, s), 6.10 (1H, m), 6.01 (2H, s), 2.97 (3H, d, J=4.8 Hz), 2.21 (3H, s).

Example 30

8-Methyl-5-(4-nitrophenyl)-7H-1,3-dioxolo-
/4,5-h//2,3/benzodiazepine-7-carboxylic
acid-(2-morpholino-4-ylethyl)amide

10.0 g (22.6 mmoles) of the compound prepared according to Example 26, 100 cm³ of ethanol and 19.08 g (146.6 mmoles) of 4-(2-aminoethyl)morpholine are transferred to an acidresistant steel bomb tube of 200 cm³ capacity. The bomb tube is sealed, and the mixture is stirred at 110 °C for 24 hours. On the next day, the bomb tube is opened, and the mixture is evaporated under reduced pressure. The evaporation residue is stirred in 400 cm³ of water for 5 hours, then extracted three times using 200 cm³ of chloroform each time. The organic phase is dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The 8.0 g of evaporation residue are transferred to a silica gel column that is eluted with a mixture of chloroform and

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methanol. The adequate fraction is evaporated, the evaporation residue is stirred in 50 cm³ of diisopropyl ether for an hour. The crystals are filtered, and washed with diisopropyl ether.

Thus, 5.8 g (35.8 %) of the title compound are obtained. M.p.: 218-220 °C.

¹H NMR (DMSO-d₆): δ 8.27 (2H, d, J=9.0 Hz), 7.88 (2H, d, J=9.0 Hz), 7.06 (1H, t, J=2.8 Hz), 6.98 (1H, s), 6.59 (1H, s), 6.31 (1H, s), 6.12 (2H, s), 3.60 (4H, m), 3.3 (2H, s), 2.5-2.1 (6H, m), 2.09 (3H, s).

Example 31

7-Guanidinocarbonyl-8-methyl-5-(4-nitrophenyl)-
-7H-1,3-dioxolo[4,5-h//2,3]benzodiazepine

8.9 g (20 mmoles) of the compound prepared according to Example 26 are suspended in 300 cm³ of absolute ethanol, and 4.0 g (40 mmoles) of 97 % guanidine hydrochloride are added. To the suspension, 2.3 g of sodium methylate are added in 15 minutes, and the mixture is boiled under stirring for 3 hours. After cooling, the suspension is filtered, and the filtrate is evaporated under reduced pressure. To the evaporation residue, 250 cm³ of water are added, and, after an hour's stirring, the crystals obtained are filtered, and washed three times using 30 cm³ of water each time. Thus, 7.6 g of crude product melting at 202-206 °C are obtained which is transferred to a

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silica gel column that is eluted with a mixture of chloroform and methanol. The adequate fraction is evaporated, the evaporation residue is crystallized in 40 cm³ of diethyl ether. The crystals are filtered, and washed with diethyl ether.

Thus, 6.1 g (74.8 %) of the title compound are obtained. M.p.: 204-206 °C.

¹H NMR (DMSO-d₆): δ 8.21 (2H, d, J=9.0 Hz), 7.82 (2H, d, J=9.0 Hz), 7.00 (1H, s), 6.50 (1H, s), 6.31 (1H, s), 6.13 (1H, s), 6.05 (1H, s), 2.22 (3H, s).

Example 32

7-(4-Benzylpiperidine-1-ylcarbonyl)-8-methyl-5-(4-nitrophenyl)-7H-1,3-dioxolo[4,5-h//2,3]-benzodiazepine

8.0 g (18 mmoles) of the compound prepared according to Example 26, 80 cm³ of ethanol and 32 cm³ (180 mmoles) of 4-benzylpiperidine are transferred to an acid-resistant steel bomb tube having 200 cm³ capacity. The bomb tube is sealed, and the mixture is stirred at 110 °C for 24 hours. Then the bomb tube is opened, and the mixture is evaporated under reduced pressure. To the evaporation residue, 250 cm³ of diethyl ether are added, and, after 2 hours' stirring, the crystals obtained are filtered and washed with diethyl ether.

Thus, 6.4 g (60.4 %) of the title compound are obtained. M.p.: 211-212.5 °C.

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^1H NMR (CDCl_3): δ 8.20 (2H, d, $J=8.8$ Hz), 7.72 (2H, d, $J=8.8$ Hz), 7.40-7.00 (5H, m), 6.69 (1H, s), 6.46 (1H, s), 6.15 (1H, s), 6.03 (2H, s), 4.00 (2H, d, $J=15$ Hz), 2.66 (2H, t, $J=13$ Hz), 2.52 (2H, d, $J=7$ Hz), 2.07 (3H, s), 1.80-1.50 (3H, m), 1.3-1.1 (2H, m).

Example 33

7-[2-/N-Benzyl-(2-morpholinoethyl)amino/-acetyl]-8-methyl-5-(4-nitrophenyl)-7H-1,3-dioxolo[4,5-h]/2,3/benzodiazepine

A mixture of 12.0 g (30 mmoles) of the compound prepared according to Example 27, 250 cm^3 of acetonitrile and 14.9 g (66 mmoles) of benzyl-(2-morpholine-4-ylethyl)amine is boiled for 7 hours. After cooling, the reaction mixture is filtered, and the filtrate is evaporated under reduced pressure. The evaporation residue is dissolved in 300 cm^3 of dichloromethane, washed twice with 100 cm^3 of water each time, and the organic phase is evaporated under reduced pressure. The evaporation residue (11.4 g) is transferred to a silica gel column that is eluted with a mixture of chloroform and methanol. The adequate fraction is evaporated under reduced pressure, then treated at a pressure of 0.1 mm Hg.

Thus, 10.0 g (57.1 %) of crystalline foam are obtained. M.p.: 69-70 $^\circ\text{C}$.

Analysis: for $\text{C}_{32}\text{H}_{33}\text{N}_5\text{O}_6$ (583.65)

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calculated: N 12.00 %;

found: N 11.82 %.

^1H NMR (CDCl_3): δ 8.23 (2H, d, $J=8.8$ Hz),
7.59 (2H, d, $J=8.8$ Hz), 7.25 (5H, m), 6.77
(1H, s), 6.44 (1H, s), 6.33 (1H, s), 6.04
(2H, s), 3.91 (3H, bs), 3.62 (5H, m), 2.93
(2H, m), 2.48 (2H, m), 2.37 (4H, m), 2.28
(3H, s).

Example 34

7-{2-[N-/2-(3,4-Dimethoxyphenyl)ethyl/-
methylamino]acetyl}-8-methyl-5-(4-nitrophenyl)-
-7H-1,3-dioxolo[4,5-h]/2,3/benzodiazepine

A mixture of 14.4 g (36 mmoles) of the compound prepared according to Example 27, 200 cm³ of acetonitrile and 15 g (76.8 mmoles) of N-/2-(3,4-dimethoxyphenyl)ethyl/methylamine is boiled for 5 hours. After cooling, the reaction mixture is evaporated under reduced pressure. The evaporation residue is crystallized in 200 cm³ of water, the crystals are filtered, washed three times using 50 cm³ of water each time, and dried under a lamp emitting infra red radiation. The crude product (19.7 g) is transferred to a silica gel column that is eluted with a mixture of chloroform and methanol. The adequate fraction is evaporated under reduced pressure, and the evaporation residue (7.0 g) is dissolved in 20 cm³ of ethyl acetate. To the solution obtained, a solution of 1.13 g (12.5 mmoles)

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tert.-butylate are added. The mixture is stirred for half an hour, then 10.95 g (27.4 mmoles) of the compound prepared according to Example 27 are added at 10 °C. The reaction mixture is stirred at 25 °C for an hour, then, 45 cm³ of water are added to it, drop by drop, under cooling. The crystals precipitated are filtered, then transferred to a silica gel column that is eluted with a mixture of hexane and acetone. The adequate fraction is evaporated under reduced pressure.

Thus, 3.47 g (28.3 %) of the title compound of yellow colour are obtained. M.p.: 235-237 °C.

¹H NMR (CDCl₃): δ 8.30 (2H, d, J=8.8 Hz), 7.70 (2H, d, J=8.8 Hz), 7.06 (1H, s), 6.63 (1H, s), 6.57 (1H, s), 6.13 (2H, bs), 4.6-4.1 (2H, m), 3.28 (2H, m), 2.26 (2H, m), 2.15 (3H, s), 1.96 (2H, m).

Example 36

7-/2-(4-Benzylpiperidiny)acetyl/-8-methyl-
-5-(4-nitrophenyl)-7H-1,3-dioxolo/4,5-h//2,3/-
benzodiazepine

A mixture of 10.0 g (25 mmoles) of the compound prepared according to Example 27, 250 cm³ of acetonitrile and 9.64 g (55 mmoles) of 4-benzyl-piperidine is boiled for 4 hours. The reaction mixture is evaporated under reduced pressure. The evaporation residue is crystallized from 250 cm³ of water, stirred

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at 25 °C for 3 hours, the crystals obtained are filtered, and washed with water. The crude product is suspended in 200 cm³ of diethyl ether, and, after 30 minutes' stirring, filtered, and washed with diethyl ether.

Thus, 10.5 g (78.0 %) of the title compound are obtained. M.p.: 102-104 °C.

Analysis: for C₃₁H₃₀N₄O₅ (538.61)

calculated: C 69.13 %, H 5.61 %, N 10.40 %;

found: C 69.27 %, H 5.72 %, N 10.16 %.

¹H NMR (CDCl₃): δ 8.26 (2H, d, J=8.8 Hz), 7.68 (2H, d, J=8.8 Hz), 7.30-7.10 (5H, m), 6.75 (1H, s), 6.46 (1H, s), 6.32 (1H, s), 6.05 (2H, bs), 3.60-3.30 (2H, m), 3.00-2.85 (2H, m), 2.50 (2H, m), 2.26 (3H, s), 2.15 (2H, m), 1.6 (3H, m), 1.3 (2H, m).

Example 37

N-[2-/8-Methyl-5-(4-nitrophenyl)-7H-1,3-dioxolo/4,5-h//2,3/benzodiazepine-7-yl/-2-oxoethyl]phthalimide

6.0 g (15.00 mmoles) of the compound prepared according to Example 27 are dissolved in 30 cm³ of dimethylformamide. To the solution, 0.9 g (5.4 mmoles) of potassium iodide and 3.75 g (20.2 mmoles) of potassium phthalimide are added. The mixture is boiled for 2 hours, then, after cooling, 45 cm³ of water are added to it, drop by drop. After an hour's stirring, the crystals obtained are filtered, and washed with water. The crude

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product is recrystallized from ethanol.

Thus, 3.58 g (46.7 %) of the title compound are obtained. M.p.: 206-209 °C.
¹H NMR (CDCl₃): δ 8.28 (2H, d, J=8.8 Hz), 7.88 (2H, d, J=8.8 Hz), 7.74 (4H, m), 6.74 (1H, s), 6.53 (1H, s), 6.30 (1H, s), 6.05 (2H, bs), 4.82 (2H, m), 2.26 (3H, s).

Example 38

8-Methyl-7-[2-/4-(2-methoxyphenyl)-piperazinyl/acetyl]-5-(4-nitrophenyl)-7H-1,3-dioxolo[4,5-h]/2,3/benzodiazepine

A mixture of 12.0 g (30 mmoles) of the compound prepared according to Example 27, 150 cm³ of acetonitrile and 12.8 g (66.6 mmoles) of 1-(2-methoxyphenyl)piperazine is boiled for 6 hours. After cooling, the reaction mixture is filtered, and the filtrate is evaporated under reduced pressure. The evaporation residue is crystallized from 150 cm³ of water, stirred at 25 °C for half an hour, the crystals obtained are filtered, and washed with water. The 16.0 g (96 %) of crude product are transferred to a silica gel column that is eluted with a mixture of hexane and acetone. The adequate fraction is evaporated under reduced pressure, the evaporation residue is crystallized from a mixture of petroleum ether (b.p.: 30-40 °C) and diethyl ether in a ratio of 2:1, and the crystals are filtered.

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Thus, 10.1 g (60.6 %) of the title compound are obtained. M.p.: 119-120 °C.
¹H NMR (CDCl₃): δ 8.28 (2H, d, J=8.8 Hz), 7.88 (2H, d, J=8.8 Hz), 7.00-6.80 (4H, m), 6.78 (1H, s), 6.50 (1H, s), 6.35 (1H, bs), 6.04 (2H, bs), 3.85 (3H, s), 3.68 (1H, m), 3.48 (1H, m), 3.10 (4H, bs), 2.85 (2H, m), 2.75 (2H, m), 2.30 (3H, s).

Example 39

8-Methyl-7-[2-/4-(3-methoxyphenyl)-piperazinyl/acetyl]-5-(4-nitrophenyl)-7H-1,3-dioxolo/4,5-h//2,3/benzodiazepine

A mixture of 4.36 g (10.9 mmoles) of the compound prepared according to Example 27, 70 cm³ of acetonitrile and 4.2 g (21.8 mmoles) of 1-(3-methoxyphenyl)piperazine is boiled for 7 hours. After cooling, the reaction mixture is filtered, and the filtrate is evaporated under reduced pressure. The evaporation residue is crystallized from 30 cm³ of water, stirred at 25 °C for half an hour, the crystals obtained are filtered, and washed with water. The 5.0 g of crude product are recrystallized from 100 cm³ of ethyl alcohol, the crystals obtained are filtered, and washed with diisopropyl ether.

Thus, 4.0 g (66.1 %) of the title compound are obtained. M.p.: 206-208 °C.
¹H NMR (CDCl₃): δ 8.28 (2H, d, J=8.8 Hz), 7.71 (2H, d, J=8.8 Hz), 7.15 (1H, t, J=8.2

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Hz), 6.77 (1H, s), 6.55-6.35 (5H, m), 6.04 (2H, bs), 3.77 (3H, s), 3.60 (2H, m), 3.20 (4H, t, J=4.6 Hz), 2.80 (4H, m), 2.30 (3H, d, J=0.9 Hz).

Example 40

(+)-7-{2-[4-/2-Hydroxy-3-(2-methoxyphenoxy)propyl/piperazinyl]acetyl}-8-methyl-5-(4-nitrophenyl)-7H-1,3-dioxolo[4,5-h/-/2,3/benzodiazepine

A mixture of 20 g (50 mmoles) of the compound prepared according to Example 27, 300 cm³ of acetonitrile and 29.0 g (108.9 mmoles) of 1-(2-methoxyphenoxy)-3-piperazine-1-yl-2-propanol is boiled for 7 hours, then further 5.1 g (19.2 mmoles) of 1-(2-methoxyphenoxy)-3-piperazine-1-yl-2-propanol are added to the mixture. The reaction mixture is boiled for further 24 hours, then cooled, and evaporated under reduced pressure. From the oily evaporation residue, twice 300 cm³ of water are decanted, then the residue is dissolved in 450 cm³ of dichloromethane, and the organic solution is washed twice using 300 cm³ of water each time. The dichloromethane phase is dried, and evaporated under reduced pressure. The evaporation residue is crystallized from 200 cm³ of water, stirred at 25 °C for 3 hours, the crystals obtained are filtered, and washed with water. The 19.2 g of crude product are transferred to a silica

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gel column that is eluted with a mixture of chloroform and methanol. The adequate fraction is evaporated, the evaporation residue is crystallized from diisopropyl ether, the crystals are filtered, and washed with diisopropyl ether.

Thus, 11.2 g (35.6 %) of the title compound are obtained. M.p.: 160-161.5 °C.
 Analysis: for $C_{33}H_{35}N_5O_8$ (629.68)
 calculated: C 62.95 %, H 5.60 %, N 11.12 %;
 found: C 63.52 %, H 5.55 %, N 11.08 %.
 1H NMR ($CDCl_3$): δ 8.28 (2H, d, $J=8.8$ Hz),
 7.69 (2H, d, $J=8.8$ Hz), 7.00-6.85 (4H, m),
 6.77 (1H, s), 6.49 (1H, s), 6.34 (1H, s),
 6.05 (2H, m), 4.15 (1H, m), 4.01 (2H, d, $J=5.2$
 Hz), 3.85 (3H, s), 3.65 (1H, m), 3.40 (1H,
 m), 2.70 (4H, m), 2.55 (6H, m), 2.23 (3H,
 d, $J=1.0$ Hz).

Example 41

8-Methyl-7-{3-[N-/2-(3,4-dimethoxyphenyl)-ethyl/methylamino]propionyl}-5-(4-nitrophenyl)-7H-1,3-dioxolo-/4,5-h//2,3/-benzodiazepine

A mixture of 14.9 g (36 mmoles) of the compound prepared according to Example 28, 200 cm³ of acetonitrile and 15.0 g (76.8 mmoles) of N-/2-(3,4-dimethoxyphenyl)ethyl/-methylamine is boiled for 3 hours. After cooling, the reaction mixture is filtered, the filtrate is evaporated under reduced

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pressure. The evaporation residue is dissolved in 400 cm³ of dichloromethane, and washed three times using 100 cm³ of water each time. The organic phase is dried, and evaporated under reduced pressure. The evaporation residue (18.5 g) is transferred to a silica gel column that is eluted with a mixture of chloroform and methanol. The adequate fraction is evaporated under reduced pressure, then treated at a pressure of 0.1 mm Hg, and the crystals are collected.

Thus, 15.3 g (74.3 %) of the title compound are obtained. M.p.: 64-66 °C.

Analysis: for C₃₁H₃₂N₄O₇ (572.62)

calculated: N 9.78 %;

found: N 9.48 %.

¹H NMR (CDCl₃): δ 8.24 (2H, d, J=8.7 Hz), 7.64 (2H, d, J=8.7 Hz), 6.80-6.70 (3H, m), 6.77 (1H, s), 6.48 (1H, s), 6.33 (1H, s), 6.04 (1H, s), 5.95 (1H, s), 3.85 (3H, s), 2.90-2.60 (8H, m), 2.37 (3H, s), 2.28 (3H, s).

Example 42

7-[3-/N-Benzyl-(2-morpholinoethyl)amino/-propionyl]-8-methyl-5-(4-nitrophenyl)-7H-1,3-dioxolo[4,5-h//2,3/- benzodiazepine

A mixture of 10.34 g (25 mmoles) of the compound prepared according to Example 28, 250 cm³ of acetonitrile and 12.42 g (55.0 mmoles) of benzyl-(2-morpholine-4-ylethyl)amine

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is boiled for 8 hours. The reaction mixture is evaporated under reduced pressure. The evaporation residue is crystallized from 150 cm³ of water, stirred at 25 °C for 2 hours, the crystals obtained are filtered, and washed with water. The crude product (10.8 g) is transferred to a silica gel column that is eluted with a mixture of chloroform and methanol. The adequate fraction is evaporated under reduced pressure, and treated at a pressure of 0.1 mm Hg. The crystals are collected.

Thus, 9.2 g (61.7 %) of the title compound are obtained. M.p.: 74-75 °C.

Analysis: for C₃₃H₃₅N₅O₆ (597.68)

calculated: C 66.32 %, H 5.90 %, N 11.72 %;

found: C 65.85 %, H 5.80 %, N 11.78 %.

¹H NMR (CDCl₃): δ 8.23 (2H, d, J=8.7 Hz), 7.59 (2H, d, J=8.7 Hz), 7.25 (5H, m), 6.75 (1H, s), 6.39 (1H, s), 6.33 (1H, s), 6.02 (2H, s), 3.65 (6H, m), 3.00-2.40 (12H, m), 2.28 (3H, d, J=1.2 Hz).

Example 43

8-Methyl-7-[3-/4-(2-methoxyphenyl)-piperazinyl/propionyl]-5-(4-nitrophenyl)-7H-1,3-dioxolo[4,5-h//2,3/benzodiazepine

A mixture of 12.4 g (30 mmoles) of the compound prepared according to Example 28, 150 cm³ of acetonitrile and 12.8 g (66.6 mmoles) of 1-(2-methoxyphenyl)piperazine is

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boiled for 2.5 hours. After cooling, the reaction mixture is filtered, and the filtrate is evaporated under reduced pressure. The evaporation residue is crystallized from 150 cm³ of water, stirred at 25 °C for 2 hours, the crystals obtained are filtered, and washed with water. The 17.0 g of crude product is heated to boiling in 120 cm³ of water, and the latter is decanted from the oil. To the residue, 50 cm³ of diisopropyl ether are added to crystallize the product. After an hour's stirring at 25 °C, the crystals obtained are filtered, and washed three times using 10 cm³ of diisopropyl ether each time.

Thus, 15.4 g (90.2 %) of the title compound are obtained. M.p.: 171-173 °C.

Analysis: for C₃₁H₃₁N₅O₆ (569.62)

calculated: N 12.29 %;

found: N 12.39 %.

¹H NMR (CDCl₃): δ 8.27 (2H, d, J=8.7 Hz), 7.75 (2H, d, J=8.7 Hz), 7.00-6.80 (4H, m), 6.77 (1H, s), 6.50 (1H, s), 6.34 (1H, bs), 6.00 (2H, m), 3.86 (3H, s), 3.30-2.60 (12H, m), 2.28 (3H, s).

Example 44

8-Methyl-7-[3-/4-(3-methoxyphenyl)-piperazinyl/propionyl]-5-(4-nitrophenyl)-7H-1,3-dioxolo/4,5-h//2,3/benzodiazepine

A mixture of 6.12 g (14.8 mmoles) of the compound prepared according to Example

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28, 100 cm³ of acetonitrile and 5.5 g (28.6 mmoles) of 1-(3-methoxyphenyl)piperazine is boiled for 7 hours. The reaction mixture is evaporated under reduced pressure. The evaporation residue is crystallized from 150 cm³ of water, stirred at 25 °C for an hour, the crystals obtained are filtered, and washed with water. The 8.0 g of crude product are transferred to a silica gel column that is eluted with a mixture of chloroform and methanol. The adequate fraction is evaporated under reduced pressure. The evaporation residue is crystallized from 85 cm³ of diethyl ether. After an hour's stirring at 25 °C, the crystals obtained are filtered, and washed three times using 10 cm³ of diethyl ether each time.

Thus, 5.06 g (60.1 %) of the title compound are obtained. M.p.: 165-166 °C.
¹H NMR (DMSO-d₆): δ 8.33 (2H, d, J=8.8 Hz), 7.77 (2H, d, J=8.8 Hz), 7.10 (2H, m), 6.68 (1H, s), 6.54 (1H, s), 6.506.30 (3H, m), 6.15 (1H, s), 6.10 (1H, s), 3.71 (3H, s), 3.40-2.60 (12H, m), 2.17 (3H, s).

Example 45

7-[3-/4-(4-Fluorophenyl)-4-hydroxy-piperidinyI/propionyl]-8-methyl-5-(4-nitrophenyl)-7H-1,3-dioxolo-4,5-h//2,3/benzodiazepine

A mixture of 12.4 g (30 mmoles) of the compound prepared according to Example 28,

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250 cm³ of acetonitrile and 12.9 g (66.1 mmols) of 4-(4-fluorophenyl)piperidine-4-ol is boiled for 2 hours. After cooling, the reaction mixture is evaporated under reduced pressure. The evaporation residue is crystallized from 300 cm³ of water, stirred at 25 °C for 2 hours, the crystals obtained are filtered, and washed with water. The 17.0 g of crude product are suspended in 100 cm³ of diisopropyl ether, and, after an hour's stirring at 25 °C, the crystals are filtered, and washed three times using 20 cm³ of diisopropyl ether each time.

Thus, 16.5 g (96.1 %) of the title compound are obtained. M.p.: 134-136 °C.

Analysis: for C₃₁H₂₉FN₄O₆ (572.60)

calculated: N 9.78 %;

found: N 9.88 %.

¹H NMR (DMSO-d₆): δ 8.33 (2H, d, J=8.8 Hz), 7.77 (2H, d, J=8.8 Hz), 7.46 (2H, m), 7.07 (3H, m), 6.61 (1H, s), 6.51 (1H, s), 6.15 (1H, s), 6.10 (1H, s), 4.90 (1H, s), 3.40-2.40 (13H, m), 2.18 (3H, s), 1.90 (2H, m), 1.60 (2H, m).

Example 46

5-(4-Aminophenyl)-8-methyl-7H-1,3-dioxolo-
/4,5-h//2,3/benzodiazepine-7-carboxylic
acid-(2-morpholino-4-ylethyl)amide

2.0 g (4.17 mmols) of the compound prepared according to Example 30 are

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transferred into a mixture of 80 cm³ of ethanol and 20 cm³ of water. To the mixture, 0.4 g of 10 % palladium/carbon catalyst, then, in 4 minutes, 4.0 cm³ (80.6 mmoles) of 98 % hydrazine hydrate are added at 15 to 20 °C. The mixture is stirred at 25 °C for 4.5 hours, the catalyst is filtered, and washed with ethanol. The filtrate is evaporated under reduced pressure, and, to the residue, 120 cm³ of water are added. After an hour's stirring, the crystals are filtered, and washed with water. The crude product is transferred to a silica gel column that is eluted with a mixture of chloroform and methanol. The adequate fraction is evaporated, and the evaporation residue is crystallized from diethyl ether. The crystals obtained are filtered, and washed with diethyl ether.

Thus, 0.52 g (27.8 %) of the title compound are obtained. M.p.: 249-251 °C.
Analysis: for C₂₄H₂₇N₅O₄ (449.51)
calculated: C 64.13 %, H 6.05 %, N 15.58 %;
found: C 64.36 %, H 6.20 %, N 15.20 %.
¹H NMR (CDCl₃): δ 7.36 (2H, d, J=8.3 Hz), 6.79 (1H, m), 6.67 (2H, s), 6.65 (2H, d, J=8.3 Hz), 6.13 (1H, s), 6.01 (1H, s), 5.95 (1H, s), 4.01 (2H, bs), 3.80 (4H, t, J=4.5 Hz), 3.5-3.3 (2H, m), 2.65-2.4 (6H, m), 2.23 (3H, s).

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Example 47

5-(4-Aminophenyl)-7-(guanidinocarbonyl)-8-methyl-7H-1,3-dioxolo[4,5-h//2,3/-benzodiazepine monohydrate

3.0 g (7.34 mmoles) of the compound prepared according to Example 31 are transferred into a mixture of 150 cm³ of methanol and 30 cm³ of water. To the mixture, 0.9 g of 10 % palladium/carbon catalyst are added, then, in 15 minutes, 6.0 cm³ (120 mmoles) of 98 % hydrazine hydrate are added at 20 to 25 °C. The mixture is stirred at 25 °C for 2.5 hours. Then, the catalyst is filtered, and washed with methanol. The filtrate is evaporated under reduced pressure, and, to the residue, 100 cm³ of water are added. After an hour's stirring, the crystals are filtered, and washed with water. The crude product is transferred to a silica gel column that is eluted with a mixture of chloroform and methanol. The adequate fraction is evaporated, and the evaporation residue is crystallized from diethyl ether. The crystals obtained are filtered, and washed with diethyl ether.

Thus, 1.54 g (55.6 %) of the title compound are obtained. M.p.: 216-218 °C.
¹H NMR (DMSO-d₆): δ 7.19 (2H, d, J=8.4 Hz), 7.1-6.65 (2H, br), 6.92 (1H, s), 6.64 (1H, s), 6.54 (2H, d, J=8.4 Hz), 6.22 (1H, s), 6.11 (1H, s), 6.04 (1H, s), 5.55 (2H, s),

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3.32 (2H, s), 2.19 (3H, s).

Example 48

5-(4-Aminophenyl)-7-/(4-benzylpiperidine-1-yl)carbonyl/-8-methyl-7H-1,3-dioxolo-4,5-h//2,3/benzodiazepine

5.0 g (9.5 mmoles) of the compound prepared according to Example 32 are dissolved in a mixture of 200 cm³ of chloroform and 90 cm³ of methanol. To the solution obtained, 5.0 g of 10 % palladium/carbon catalyst suspended in 10 cm³ of methanol are added, and the mixture is vigorously stirred under hydrogen atmosphere at room temperature. The reduction is finished in 16 hours. The catalyst is filtered, washed three times using 50 cm³ of methanol each time, and the filtrate is evaporated under reduced pressure. The evaporation residue is transferred to a silica gel column that is eluted with a mixture of chloroform and methanol. The adequate fraction is evaporated under reduced pressure. To the residue, 20 cm³ of diethyl ether are added, and the mixture is stirred for an hour. The crystals obtained are filtered, washed three times using 10 cm³ of diethyl ether each time, and dried under a lamp emitting infra red radiation.

Thus, 1.4 g (32.6 %) of the title compound are obtained. M.p.: 179-181 °C.

Analysis: for C₃₀H₃₀N₄O₃ (494.60):

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calculated: N 11.33 %;

found: N 11.06 %.

^1H NMR (CDCl_3): δ 7.67 (1H, s), 7.4-7.2 (4H, m), 7.2-7.05 (4H, m), 6.87 (1H, s), 6.80 (1H, d, $J=2.4$ Hz), 6.78 (1H, d, $J=2.4$ Hz), 6.08 (2H, s), 4.20 (2H, br), 4.10 (2H, m), 2.72 (3H, s), 2.70-2.55 (1H, m), 2.50-2.45 (1H, m), 2.43 (2H, d, $J=7.2$ Hz), 1.6 (1H, m), 1.5 (1H, m), 1.4 (1H, m), 1.1-0.95 (1H, m), 0.85-0.70 (1H, m).

Example 49

5-(4-Aminophenyl)-8-methyl-7-/2-(2-morpholino-ethylamino)acetyl/-7H-1,3-dioxolo/4,5-h//2,3/-benzodiazepine monohydrate

6.0 g (10.3 mmoles) of the compound prepared according to Example 33 are transferred into a mixture of 240 cm^3 of methanol and 50 cm^3 of water. To the mixture, 4.8 g of 10 % palladium/carbon catalyst, then, in 20 minutes, 24.0 cm^3 (484 mmoles) of 98 % hydrazine hydrate are added at 20 to 25 $^\circ\text{C}$. The mixture is stirred at 25 $^\circ\text{C}$ for 100 hours, then further 2.4 g of 10 % palladium/carbon catalyst and 12.0 cm^3 (242 mmoles) of 98 % hydrazine hydrate are added. After further 72 hours' stirring, the catalyst is filtered, washed with methanol, and the filtrate is evaporated under reduced pressure. To the residue, 100 cm^3 of water and 150 cm^3 of dichloromethane are added. After 5 minutes'

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stirring, the phases are separated, the aqueous phase is still extracted twice with 150 cm³ of dichloromethane each time. The organic phase is dried, and evaporated under reduced pressure. The evaporation residue is transferred to a silica gel column that is eluted with a mixture of chloroform and methanol. The adequate fraction is evaporated, and the evaporation residue is crystallized from diisopropyl ether. The crystals obtained are filtered, and washed with diisopropyl ether.

Thus, 3.65 g (76.7 %) of the title compound are obtained. M.p.: 92-94 °C.

Analysis: for C₂₅H₂₉N₅O₄·H₂O (481.56)

calculated: N 14.54 %;

found: N 14.25 %.

¹H NMR (DMSO-d₆): δ 7.18 (2H, d, J=8.4 Hz), 7.00 (1H, s), 6.72 (1H, s), 6.58 (2H, d, J=8.4 Hz), 6.48 (1H, s), 6.15 (1H, s), 6.08 (1H, s), 5.75 (2H, bs), 3.73 (1H, d, J=16.9 Hz), 3.54 (4H, t, J=4.6 Hz), 3.30 (1H, d, J=16.9 Hz), 3.05 (1H, m), 2.62 (2H, t, J=6.0 Hz), 2.40-2.25 (6H, m), 2.16 (3H, s).

Example 50

5-(4-Aminophenyl)-7-{2-[N-/2-(3,4-dimethoxyphenyl)ethyl/methylamino]acetyl}-8-methyl-7H-1,3-dioxolo[4,5-h]/2,3/benzodiazepine

7.0 g (12.5 mmol) of the compound prepared according to Example 34 are added :

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to a mixture of 400 cm³ of ethanol and 84 cm³ of water. To the mixture, 2.8 g of 10 % palladium/carbon catalyst, and, in 30 minutes, 17.5 cm³ (353 mmoles) of 98 % hydrazine hydrate are added at 20 to 25 °C. The mixture is stirred at 25 °C for 73 hours. Then, the catalyst is filtered, washed with ethanol, and the filtrate is evaporated under reduced pressure. To the residue, 80 cm³ of water are added. After an hour's stirring, the crystals are filtered, and washed with water. The crude product is suspended in diisopropyl ether, then filtered, and washed with diisopropyl ether.

Thus, 3.95 g (59.8 %) of the title compound are obtained. M.p.: 88-90 °C.

Analysis: for C₃₀H₃₂N₄O₅ (528.59)

calculated: N 10.60 %;

found: N 10.32 %.

¹H NMR (CDCl₃): δ 7.32 (2H, d, J=8.6 Hz), 6.80-6.67 (5H, m), 6.65 (2H, d, J=8.6 Hz), 6.31 (1H, s), 6.03 (1H, s), 5.96 (1H, s), 3.98 (2H, bs), 3.83 (6H, s), 3.79 (1H, d, J=16.2 Hz), 3.41 (1H, d, J=16.2 Hz), 2.85-2.65 (4H, m), 2.46 (3H, s), 2.28 (3H, s).

Example 51

5-(4-Aminophenyl)-8-methyl-7-[2-/4-(2-methoxyphenyl)piperazinyl/acetyl]-7H-1,3-dioxolo/4,5-h//2,3/benzodiazepine

5.5 g (9.9 mmoles) of the compound

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(8H, m), 2.20 (3H, s), 2.13 (3H, d, J=1.0 Hz).

Example 54

5-(4-Aminophenyl)-7-[3-/N-benzyl-(2-morpholinoethylamino)/propionyl]-8-methyl-7H-1,3-dioxolo[4,5-h]/2,3/benzodiazepine

5.2 g (8.7 mmol) of the compound prepared according to Example 42 are added to a mixture of 175 cm³ of methanol and 35 cm³ of water. To the mixture, 1.4 g of 10% palladium/carbon catalyst, and, in 10 minutes, 7.0 cm³ (141 mmol) of 98% hydrazine hydrate are added at 20 to 25 °C. The mixture is stirred at 25 °C for 24 hours. Then, the catalyst is filtered, washed with methanol, and the filtrate is evaporated under reduced pressure. To the residue, 100 cm³ of water and 150 cm³ of dichloromethane are added. After 5 minutes' stirring, the phases are separated, and the aqueous phase is still twice extracted with 150 cm³ of dichloromethane each time. The organic phase is dried, evaporated under reduced pressure, and the evaporation residue is transferred to a silica gel column that is eluted with a mixture of chloroform and methanol. The appropriate fraction is evaporated, and the evaporation residue is crystallized from diisopropyl ether. The crystals obtained are filtered, and washed with diisopropyl ether.

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Thus, 0.4 g (8.2 %) of the title compound are obtained (thin-layer chromatography: using a mixture of ethanol and ammonia in a ratio of 9:1, R_f = 0.75).

M.p.: 114-116 °C.

^1H NMR (CDCl_3): δ 7.31 (2H, d, $J=8.7$ Hz), 7.26 (5H, m), 6.72 (1H, s), 6.64 (2H, d, $J=8.7$ Hz), 6.62 (1H, s), 6.31 (1H, d, $J=1.6$ Hz), 6.05 (1H, d, $J=1.6$ Hz), 5.97 (1H, d, $J=1.6$ Hz), 3.98 (2H, s), 3.64 (6H, m), 2.93-2.68 (4H, m), 2.63 (2H, m), 2.44 (2H, m), 2.36 (4H, m), 2.25 (3H, s).

Example 55

5-(4-Aminophenyl)-8-methyl-7-/3-(2-morpholino-ethylamino)propionyl/-7H-1,3-dioxolo/4,5-h/-/2,3/benzodiazepine

When the compound prepared according to Example 42 is reduced by the method of Example 54, the debenzyl derivative of the compound according to Example 54 is also formed in the reaction. The two compounds are separated by the above column chromatographic method. The appropriate fraction is evaporated, and the evaporation residue is crystallized from diisopropyl ether. The crystals obtained are filtered, and washed with diisopropyl ether.

Thus, 0.7 g (16.9 %) of the title compound are obtained (thin-layer chromatography: using a mixture of ethanol and ammonia in a ratio

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of 9:1, $R_f = 0.65$).

M.p.: 122-124 °C.

Analysis: for $C_{26}H_{31}N_5O_4$ (477.57)

calculated: N 14.66 %;

found: N 14.46 %.

1H NMR ($CDCl_3$): δ 7.32 (2H, d, $J=8.6$ Hz),
6.67 (2H, s), 6.64 (2H, d, $J=8.6$ Hz), 6.32
(1H, d, $J=1.1$ Hz), 6.04 (1H, d, $J=1.1$ Hz),
5.97 (1H, d, $J=1.1$ Hz), 4.10 (2H, bs), 3.68
(4H, t, $J=4.7$ Hz), 3.2-2.5 (8H, m), 2.43 (4H,
t, $J=4.6$ Hz), 2.27 (3H, d, $J=1.1$ Hz).

Example 56

5-(4-Aminophenyl)-8-methyl-7-[3-/4-(2-
-methoxyphenyl)piperazinyl/propionyl]-7H-
-1,3-dioxolo/4,5-h//2,3/benzodiazepine

10.2 g (17.9 mmoles) of the compound prepared according to Example 43 are added to a mixture of 300 cm³ of ethanol and 60 cm³ of water. To the mixture, 4.0 g of 10 % palladium/carbon catalyst, and, in 20 minutes, 20 cm³ (404 mmoles) of 98 % hydrazine hydrate are added at 20-25 °C. The mixture is stirred at 25 °C for 24 hours. Then, the catalyst is filtered, and washed with ethanol. The filtrate is evaporated under reduced pressure. To the residue, 200 cm³ of water are added. After an hour's stirring, the crystals are filtered, and washed with water. The crude product is transferred to a silica gel column that is eluted with a mixture of

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chloroform and methanol. The appropriate fraction is evaporated, the evaporation residue is crystallized from diisopropyl ether. The crystals obtained are filtered, and washed with diisopropyl ether.

Thus, 1.15 g (11.9 %) of the title compound are obtained. M.p.: 190-194 °C.
¹H NMR (CDCl₃): δ 7.35 (2H, d, J(8.7 Hz). 7.1-6.8 (4H, m), 6.74 (1H, s), 6.73 (1H, s), 6.64 (2H, d, J=8,7 Hz), 6.32 (1H, d, J=1.2 Hz), 6.02 (1H, d, J=1.1 Hz), 5.93 (1H, d, J=1.1 Hz), 4.00 (2H, bs), 3.85 (3H, s), 3.07 (4H, m), 3.0-2.7 (4H, m), 2.69 (4H, m), 2.28 (3H, d, J=1.1 Hz).

Example 57

5-(4-Aminophenyl)-8-methyl-7-[3-/4-(3-methoxyphenyl)piperazinyl/propionyl]-7H-1,3-dioxolo/4,5-h//2,3/benzodiazepine

5.0 g (8.8 mmoles) of the compound prepared according to Example 44 are added to a mixture of 250 cm³ of ethanol and 50 cm³ of water. To the mixture, 1.5 g of 10 % palladium/carbon catalyst, and, in 10 minutes, 8 cm³ (160 mmoles) of 98 % hydrazine hydrate are added at 20 to 25 °C. The mixture is stirred at 25 °C for 5 hours, then, the catalyst is filtered, washed with ethanol, and the filtrate is evaporated under reduced pressure. To the residue, 100 cm³ of water are added. After an hour's stirring, the

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crystals are filtered, and washed with water. The crude product is transferred to a silica gel column that is eluted with a mixture of hexane and acetone. The appropriate fraction is evaporated, and the evaporation residue is crystallized from diisopropyl ether. The crystals obtained are filtered, and washed with diisopropyl ether.

Thus, 2.9 g (61.2 %) of the title compound are obtained. M.p.: 105-106.5 °C.

Analysis: for $C_{31}H_{33}N_5O_4 \cdot H_2O$ (557.66)

calculated: C 66.76 %, H 6.33 %, N 12.56 %;

found: C 66.57 %, H 6.24 %, N 12.54 %.

1H NMR ($CDCl_3$): δ 7.34 (2H, d, $J=8.5$ Hz), 7.14 (1H, t, $J=8.1$ Hz), 6.72 (1H, s), 6.71 (1H, s), 6.62 (2H, d, $J=8.5$ Hz), 6.51 (1H, dd, $J=8.3$ and 2.3 Hz), 6.44 (1H, t, $J=2,3$ Hz), 6.40 (1H, dd, $J=8.0$ and 2.3 Hz), 6.31 (1H, d, $J=0.8$ Hz), 6.00 (1H, d, $J=1.2$ Hz), 5.92 (1H, d, $J=1.2$ Hz), 4.04 (2H, s), 3.77 (3H, s), 3.14 (4H, t, $J=4.8$ Hz), 3.0-2.7 (4H, m), 2.61 (4H, t, $J=4.8$ Hz), 2.27 (3H, d, $J=1.2$ Hz).

Example 58

5-(4-Aminophenyl)-7-[3-/4-(4-fluorophenyl)-4-hydroxypiperidine-1-yl/propionyl]-8-methyl-7H-1,3-dioxolo[4,5-h]/2,3/benzodiazepine

9.0 g (15.7 mmoles) of the compound prepared according to Example 45 are added to a mixture of 360 cm³ of ethanol and 70

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cm³ of water. To the mixture, 3.6 g of 10 % palladium/carbon catalyst, and, in 20 minutes, 18 cm³ (363 mmoles) of 98 % hydrazine hydrate are added at 20 to 25 °C. The mixture is stirred at 25 °C for 68 hours. Then, the catalyst is filtered, washed with ethanol, and the filtrate is evaporated under reduced pressure. To the residue, 200 cm³ of water are added. After 2 hours' stirring, the crystals are filtered, and washed with water. The crude product is transferred to a silica gel column that is eluted with a mixture of hexane and acetone. The appropriate fraction is evaporated, and the evaporation residue is crystallized from diisopropyl ether. The crystals obtained are filtered, and washed with diisopropyl ether.

Thus, 3.47 g (40.87 %) of the title compound are obtained. M.p.: 130-132 °C.
Analysis: for C₃₁H₃₁FN₄O₄ (542.62)
calculated: C 68.62 %, H 5.76 %, N 10.33 %;
found: C 68.52 %, H 5.88 %, N 10.12 %.
¹H NMR (DMSO-d₆): δ 7.47 (2H, m), 7.21 (2H, d, J=8.6 Hz), 7.10 (2H, m), 6.99 (1H, s), 6.72 (1H, s), 6.59 (2H, d, J=8.6 Hz), 6.46 (1H, s), 6.14 (1H, s), 6.05 (1H, s), 5.71 (2H, s), 4.82 (1H, s), 2.67 (6H, m), 2.43 (2H, m), 2.16 (3H, s), 1.85 (2H, m), 1.57 (2H, m).

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Example 59

5-(4-Aminophenyl)-7-(2-chloroacetyl)-8-methyl-
-7H-1,3-dioxolo[4,5-h]/2,3/benzodiazepine

4.0 g (10 mmoles) of the compound prepared according to Example 27 are transferred into 160 cm³ of ethanol, 9.0 g (40 mmoles) of crystalline tin(II) chloride (SnCl₂·2H₂O) are added, and the mixture is boiled for 1.5 hours. After cooling, the reaction mixture is evaporated. To the residue, 120 cm³ of water are added, and the mixture is extracted three times using 100 cm³ of dichloromethane each time. The combined dichloromethane layers are washed twice with 30 cm³ of 5 % aqueous sodium hydroxide solution each time, and twice with 150 cm³ of water each time, then dried, and evaporated under reduced pressure. To the evaporation residue, 50 cm³ of diisopropyl ether are added. After 30 minutes' stirring, the crystals are filtered.

Thus, 1.9 g (51.6 %) of the title compound are obtained. M.p.: 197-199 °C.

¹H NMR (CDCl₃ + DMSO-d₆): δ 7.27 (2H, d, J=8.6 Hz), 6.75 (1H, s), 6.72 (1H, s), 6.65 (2H, d, J=8.6 Hz), 6.35 (1H, s), 6.02 (2H, bs), 4.59 (2H, bs), 4.35 (2H, m), 2.25 (3H, d, J=1.0 Hz).

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Example 60

5-(4-Aminophenyl)-7-(3-chloropropionyl)-8-
-methyl-7H-1,3-dioxolo[4,5-h//2,3/-
benzodiazepine

6.18 g (15 mmoles) of the compound prepared according to Example 28 are transferred into 180 cm³ of ethanol, 16.92 g (75 mmoles) of crystalline tin(II) chloride (SnCl₂·2H₂O) are added, and the mixture is boiled for 70 minutes. After cooling, the reaction mixture is evaporated under reduced pressure. To the residue, 200 cm³ of water are added, and the pH of the solution is adjusted to 11 by the addition of 10 % aqueous sodium hydroxide solution. The mixture is extracted five times using 200 cm³ of dichloromethane each time. The combined dichloromethane layers are washed twice with 250 cm³ of water each time, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. To the evaporation residue, 100 cm³ of diisopropyl ether are added. After 60 minutes' stirring, the crystals are filtered, and washed with diisopropyl ether. The crude product is recrystallized from ethanol.

Thus, 1.75 g (30.7 %) of the title compound are obtained. M.p.: 162-165 °C.
Analysis: for C₂₀H₁₈ClN₃O₃ (383.84)
calculated: N 10.95 %;
found: N 10.65 %.

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^1H NMR (CDCl_3): δ 7.33 (2H, d, $J=8.7$ Hz), 6.73 (2H, s), 6.66 (2H, d, $J=8.7$ Hz), 6.33 (1H, d, $J=1.3$ Hz), 6.05 (1H, d, $J=1.3$ Hz), 5.98 (1H, d, $J=1.3$ Hz), 4.02 (2H, bs), 3.85 (1H, m), 3.75 (1H, m), 2.90 (1H, m), 2.27 (3H, d, $J=1.3$ Hz).

Example 61

5-(4-Aminophenyl)-8-methyl-7-methylcarbamoyl-7H-1,3-dioxolo[4,5-h]/2,3/benzodiazepine

4.0 g (10.5 mmoles) of the compound prepared according to Example 29 are transferred into 200 cm^3 of ethanol, 10.64 g (47.2 mmoles) of crystalline tin(II) chloride ($\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$) are added, and the mixture is boiled for 2 hours. After cooling, the reaction mixture is evaporated under reduced pressure. To the residue, 150 cm^3 of water are added, and the pH of the solution is adjusted to 11 by the addition of 10 % aqueous sodium hydroxide solution. The mixture is extracted three times using 300 cm^3 of dichloromethane each time. The combined dichloromethane layers are dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. To the evaporation residue, 30 cm^3 of diisopropyl ether are added. After 60 minutes' stirring, the crystals are filtered, and washed with diisopropyl ether.

Thus, 1.02 g (27.7 %) of the title compound are obtained. M.p.: 188-190 $^\circ\text{C}$.

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^1H NMR (CDCl_3): δ 7.27 (2H, d, $J=8.6$ Hz), 6.66 (1H, s), 6.65 (1H, s), 6.62 (2H, d, $J=8.6$ Hz), 6.13 (1H, d, $J=1.0$ Hz), 6.05 (1H, m), 6.00 (1H, s), 5.94 (1H, s), 3.7 (2H, bs), 2.92 (3H, d, $J=5.0$ Hz), 2.22 (3H, d, $J=1.2$ Hz).

Example 62

1- \square 2-/5-(4-Aminophenyl)-8-methyl-7H-1,3-dioxolo/4,5-h//2,3/benzodiazepine-7-yl/-2-oxoethyl \square pyrrolidine-2-one monohydrate

2.56 g (5.7 mmol) of the compound prepared according to Example 35 are transferred into 100 cm³ of methanol, 6.4 g (28.4 mmol) of crystalline tin(II) chloride ($\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$) are added, and the mixture is boiled for 2 hours. After cooling, the reaction mixture is evaporated under reduced pressure. To the residue, 100 cm³ of water are added, and the pH of the solution is adjusted to 11 by the addition of 10 % aqueous sodium hydroxide solution. The mixture is extracted three times using 300 cm³ of dichloromethane each time. The combined dichloromethane phases are washed with 250 cm³ of water each time, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. To the evaporation residue, 30 cm³ of diethyl ether are added. After 60 minutes' stirring, the crystals are filtered, and washed with diethyl ether.

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Thus, 2.14 g (85.9 %) of the title compound are obtained. M.p.: 103-105 °C.
 ^1H NMR (CDCl_3): δ 7.33 (2H, d, $J=8.6$ Hz), 6.73 (1H, s), 6.71 (1H, s), 6.63 (2H, d, $J=8.6$ Hz), 6.28 (1H, d, $J=1.2$ Hz), 6.04 (1H, bs), 5.98 (1H, bs), 4.57 (1H, d, $J=17.0$ Hz), 4.19 (1H, d, $J=17.0$ Hz), 3.99 (2H, bs), 3.49 (2H, t, $J=7.2$ Hz), 2.42 (2H, t, $J=8.1$ Hz), 2.26 (3H, s), 2.04 (2H, m).

Example 63

N-[2-/5-(4-Aminophenyl)-8-methyl-7H-1,3-dioxolo/4,5-h//2,3/benzodiazepine-7-yl/-2-oxoethyl]phthalimide

4.02 g (7.9 mmol) of the compound prepared according to Example 37 are transferred into 400 cm^3 of methanol, 8.9 g (39.4 mmol) of crystalline tin(II) chloride ($\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$) are added, and the mixture is boiled for 72 hours. After cooling, the reaction mixture is evaporated under reduced pressure. To the residue, 200 cm^3 of water are added, and the pH of the solution is adjusted to 11 by the addition of 10 % aqueous sodium hydroxide solution. The mixture is extracted three times using 300 cm^3 of dichloromethane each time. The combined dichloromethane layers are washed twice using 250 cm^3 of water each time, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. To the evaporation

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residue, 30 cm³ of diethyl ether are added. After 60 minutes' stirring, the crystals are filtered, and washed with diethyl ether. The crude product is transferred to a silica gel column that is eluted with a mixture of hexane and acetone. The appropriate fraction is evaporated, and the residue is stirred in 30 cm³ of diethyl ether for half an hour. The crystals obtained are filtered.

Thus, 1.52 g (40.2 %) of the title compound are obtained. M.p.: 189-191 °C. ¹H NMR (CDCl₃): δ 7.85 (2H, m), 7.70 (2H, m), 7.36 (2H, d, J=8.6 Hz), 6.77 (1H, s), 6.70 (1H, s), 6.66 (2H, d, J=8.6 Hz), 6.27 (1H, s), 6.04 (1H, s), 6.00 (1H, s), 5.06 (1H, d, J=16.1 Hz), 4.51 (1H, d, J=16.1 Hz), 3.9 (2H, br), 2.25 (3H, d, J=0.8 Hz).

Example 64

5-(4-Aminophenyl)-8-methyl-7-[2-/4-(3-methoxyphenyl)piperazinyl/acetyl]-7H-1,3-dioxolo/4,5-h//2,3/benzodiazepine dihydrate

4.0 g (7.2 mmoles) of the compound prepared according to Example 39 are transferred into 100 cm³ of ethanol, 8.11 g (36 mmoles) of crystalline tin(II) chloride (SnCl₂·2H₂O) are added, and the mixture is boiled for 7.5 hours. After cooling, the reaction mixture is evaporated under reduced pressure. To the residue, 100 cm³ of water are added, and the pH of the solution is

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adjusted to 11 by the addition of 10 % aqueous sodium hydroxide solution. The mixture is extracted three times using 300 cm³ of dichloromethane each time. The combined dichloromethane layers are dried, and evaporated under reduced pressure. To the evaporation residue, 30 cm³ of diethyl ether are added. After 30 minutes' stirring, the crystals are filtered. The crude product is transferred to a silica gel column that is eluted with a mixture of chloroform and methanol. The appropriate fraction is evaporated, and the residue is stirred in 30 cm³ of diethyl ether. The crystals obtained are filtered.

Thus, 0.25 g (6.6 %) of the title compound are obtained. M.p.: 148-150 °C.

Analysis: for C₃₀H₃₁N₅O₄·2H₂O (561.64)

calculated: C 64.16 %, H 6.28 %, N 12.47 %;

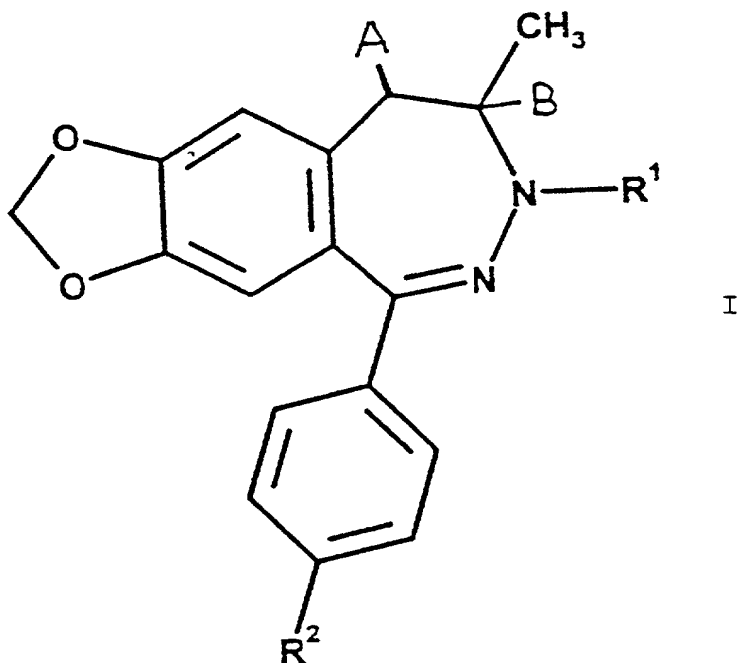
found: C 64.66 %, H 6.56 %, N 12.33 %.

¹H NMR (CDCl₃): δ 7.32 (2H, d, J=8.7 Hz), 7.14 (1H, t, J=8.1 Hz), 6.73 (2H, s), 6.66 (2H, d, J=8.7 Hz), 6.51 (1H, dd, J=8.0 and 1.8 Hz), 6.42 (2H, m), 6.33 (1H, d, J=1.1 Hz), 6.03 (1H, s), 5.99 (1H, s), 3.99 (2H, bs), 3.78 (3H, s), 3.69 (1H, d, J=15.6 Hz), 3.37 (1H, d, J=15.6 Hz), 3.20 (4H, t, J=5.0 Hz), 2.74 (4H, m), 2.29 (3H, d, J=1.1 Hz).

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Claims:

1. A 1,3-dioxolo/4,5-h//2,3/benzodiazepine derivative of the formula I



wherein

A represents a hydrogen atom,

B means a hydrogen atom,

R¹ stands for a group of the formula

$-(CH_2)_n-CO-(CH_2)_m-R$, wherein

R represents a halo atom, a pyridyl group or a group of the formula $-NR^3R^4$, wherein R³ and R⁴ mean, independently, a hydrogen atom, a C₃₋₆ cycloalkyl group, a C₁₋₄ alkoxy group, an amino group, a phenyl group optionally substituted by one or two C₁₋₄ alkyl group(s), a C₁₋₄ alkyl group which latter is

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R^7 and R^8 mean, independently, a hydrogen atom, a guanyl group, a C_{3-6} cycloalkyl group or a C_{1-4} alkyl group which latter is optionally substituted by a phenyl group or a saturated heterocyclic group having 5 or 6 members and comprising one or more nitrogen atom(s) or a nitrogen and an oxygen atom as the heteroatom, wherein the phenyl group is optionally substituted by 1 to 3 identical or different substituent(s), wherein the substituent is a C_{1-4} alkoxyl group, or

R^7 and R^8 form together with the adjacent nitrogen atom an oxopyrrolidinyl group, a phthalimido group which latter is optionally substituted, or a saturated heterocyclic group having 5 or 6 members and comprising one or more nitrogen atom(s) or a nitrogen and an oxygen atom as the heteroatom, and said heterocyclic group is optionally substituted by 1 to 3 identical or different substituent(s) selected from the group consisting of a hydroxy group, a phenyl group, a phenoxy group, a phenyl(C_{1-4} alkyl) group or a phenoxy(C_{1-4} alkyl) group, wherein in case of the substituents listed the phenyl or phenoxy group is

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the piperazinyl group is substituted by
a methoxyphenyl group,
n has a value of 0 or 1,
m has a value of 0 or 1,
R² stands for a nitro group or an amino group,
A represents a hydrogen atom,
B means a hydrogen atom,
and pharmaceutically suitable acid addition
salts thereof.

4. A 1,3-dioxolo/4,5-h//2,3/benzodiazepine
derivative as claimed in Claim 3, wherein
R³ represents a hydrogen atom,
R⁴ stands for a cyclopropyl group, a methoxy
group or an amino group,
n has a value of 0,
m has a value of 0,
R² means an amino group,
A represents a hydrogen atom,
B means a hydrogen atom,
and pharmaceutically suitable acid addition
salts thereof.

5. A 8-methyl-7H-1,3-dioxolo/4,5-h//2,3/-
benzodiazepine derivative as claimed in Claim
1, wherein in formula I
A forms together with B a valence bond
between the carbon atoms in positions
8 and 9,
R¹ represents a group of the formula
-CO-(CH₂)_p-R⁶, wherein
R⁶ stands for a halo atom, a phenoxy group,
a C₁₋₄ alkoxy group or a group of the
formula -NR⁷R⁸, wherein

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benzodiazepine derivative as claimed in Claim 5, wherein

A forms together with B a valence bond between the carbon atoms in positions 8 and 9,

R^2 represents a nitro group or an amino group,
 R^1 stands for a group of the formula

$-\text{CO}-(\text{CH}_2)_p-\text{R}^6$, wherein

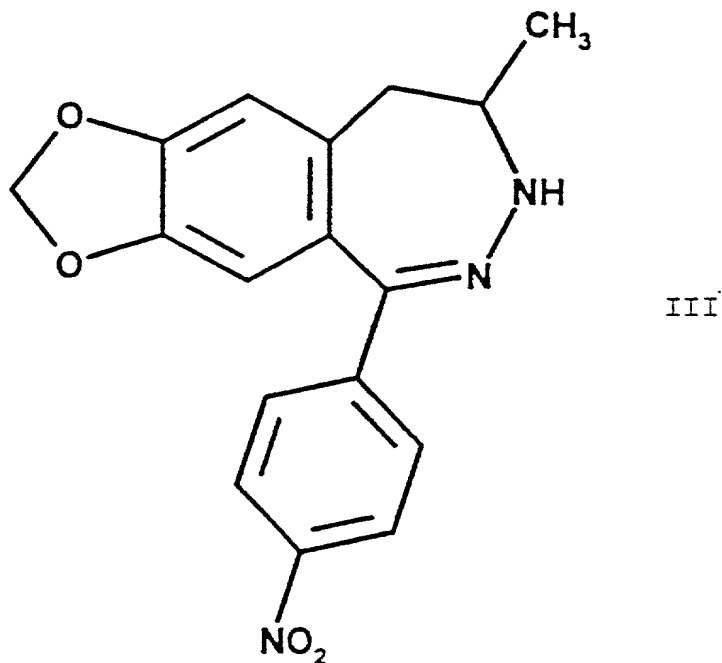
R^6 means a chloro atom, a phenoxy group, or a group of the formula $-\text{NR}^7\text{R}^8$, wherein R^7 and R^8 represent, independently, a hydrogen atom, a guanyl group or a C_{1-3} alkyl group optionally substituted by a phenyl group, a dimethoxyphenyl group or a morpholino group, or

R^7 and R^8 form with the adjacent nitrogen atom an oxopyrrolidinyl group, a phthalimido group or a saturated heterocyclic group having 5 or 6 members and comprising one or two nitrogen atom(s) or a nitrogen and an oxygen atom as the heteroatom, and said heterocyclic group is optionally substituted by one or two identical or different substituent(s) selected from the group consisting of a hydroxy group, a methoxyphenyl group, a fluorophenyl group, a benzyl group or a (methoxyphenoxy)-(hydroxypropyl) group, _____

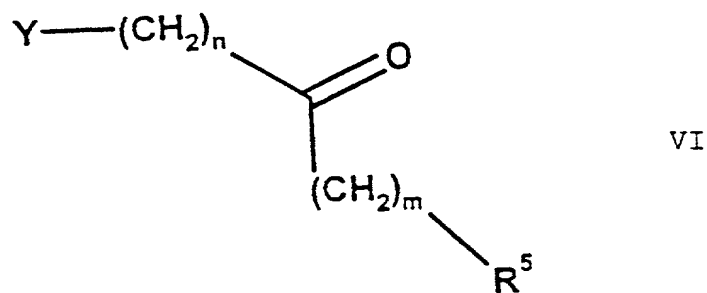
p has a value of 0, 1 or 2,

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is reacted with a reagent of the formula VI



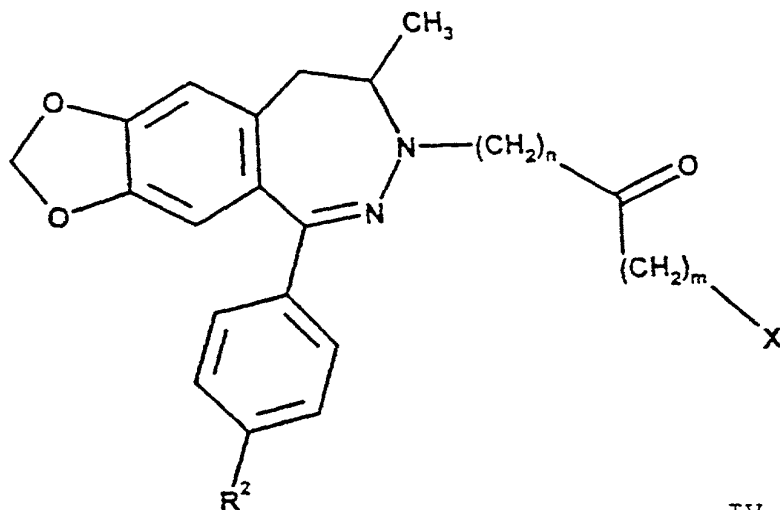
wherein Y represents a leaving group, R^5 is a halo atom or a pyridyl group; or

b) for the preparation of a compound of the formula I, wherein R^1 represents a group of the formula $-(CH_2)_n-CO-(CH_2)_m-R$, wherein R stands for an imidazolyl group, n has a value of 0, m has a value of 0, R^2 means a nitro group, A and B represent a

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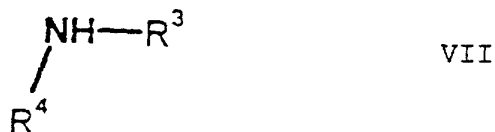
hydrogen atom, the 7,8-dihydro-8-methyl-5-(4-nitrophenyl)-9H-1,3-dioxolo[4,5-h//2,3/-benzodiazepine of the formula III is reacted with 1,1'-carbonyldiimidazole; or

c) for the preparation of a compound of the formula I, wherein R^1 represents a group of the formula $-(CH_2)_n-CO-(CH_2)_m-R$, wherein R stands for a group of the formula $-NR^3R^4$, wherein R^3 , R^4 , n and m are as defined in connection with formula I, R^2 means a nitro group, A and B represent a hydrogen atom, the 7,8-dihydro-8-methyl-5-(4-nitrophenyl)-9H-1,3-dioxolo[4,5-h//2,3/-benzodiazepine of the formula III is reacted with a reagent of the formula VI, wherein Y and R^5 represent, independently, a leaving group, n and m are as stated above, and the obtained benzodiazepine derivative of the formula IV



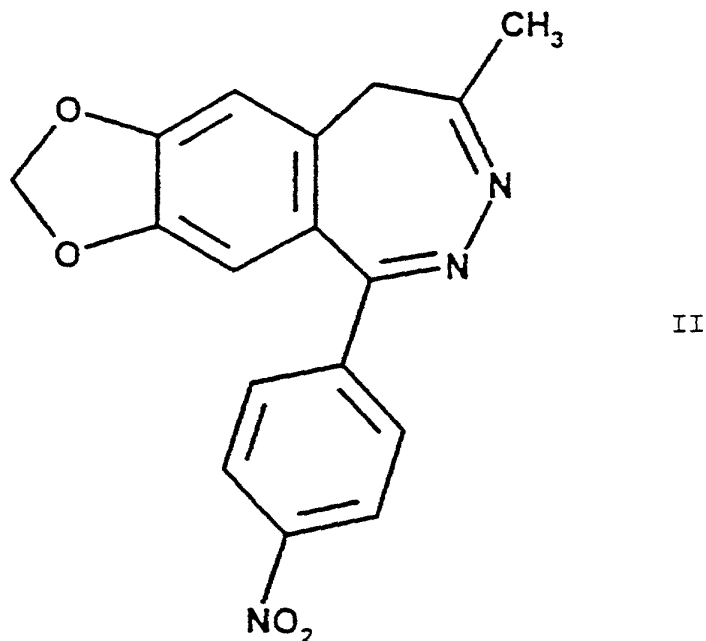
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wherein X stands for a leaving group, n and m are as stated above, is reacted with an amine of the formula VII

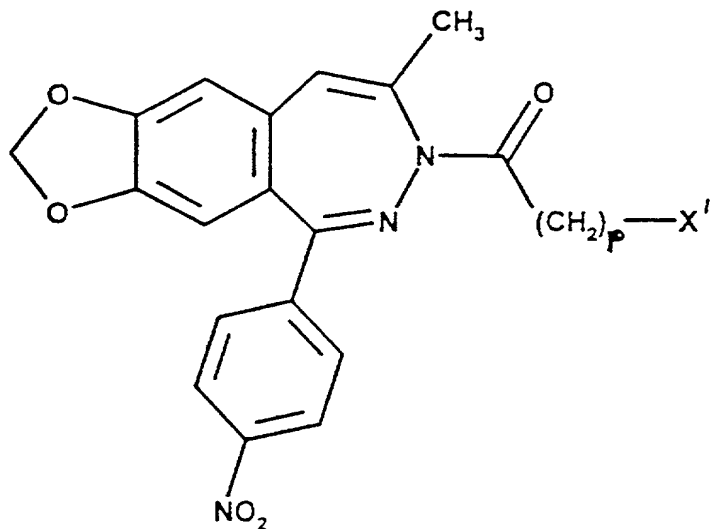


wherein R^3 and R^4 are as stated above; or

d) for the preparation of a compound of the formula I, wherein R^1 stands for a group of the formula $-\text{CO}-(\text{CH}_2)_p-\text{R}^6$, wherein R^6 represents a halo atom, a phenoxy group or a C_{1-4} alkoxy group, p has a value of 0, 1 or 2, A forms together with B a valence bond, R^2 means a nitro group, the 8-methyl-5-(4-nitrophenyl)-9H-1,3-dioxolo[4,5-h][2,3]-benzodiazepine of the formula II



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VIII

wherein X' and p are as defined above, is reacted with an amine of the formula HNR^7R^8 , wherein R^7 and R^8 are as stated above;

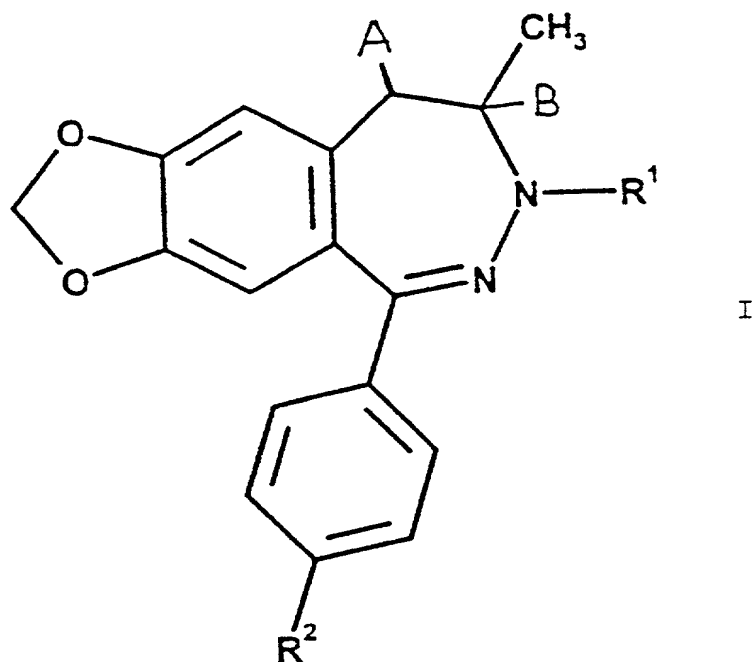
and, if desired, an obtained compound of the formula I, wherein R^2 represents a nitro group, R^1 , A and B are as defined in connection with the formula I, is transformed into a compound of the formula I, wherein R^2 stands for an amino group, by reduction;

and, if desired, an obtained compound of the formula I, wherein R^2 represents an amino group, R^1 , A and B are as defined in connection with the formula I, is reacted with a C_{1-4} alkanecarboxylic acid or a reactive acylating derivative thereof;

and, if desired, an obtained base of the formula I is converted to a pharmaceutically suitable acid addition salt or liberated from the acid addition salt.

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9. A pharmaceutical composition comprising a 1,3-dioxolo/4,5-h//2,3/benzodiazepine derivative of the formula I



wherein

A represents a hydrogen atom,

B means a hydrogen atom,

R^1 stands for a group of the formula

$-(CH_2)_n-CO-(CH_2)_m-R$, wherein

R represents a halo atom, a pyridyl group or a group of the formula $-NR^3R^4$, wherein R^3 and R^4 mean, independently, a hydrogen atom, a C_{3-6} cycloalkyl group, a C_{1-4} alkoxy group, an amino group, a phenyl group optionally substituted by one or two C_{1-4} alkyl group(s), a C_{1-4} alkyl group which latter is

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optionally substituted by a phenyl group or a saturated heterocyclic group having 5 or 6 members and comprising 1 to 3 nitrogen atom(s) or a nitrogen atom and an oxygen atom as the heteroatom, and said heterocyclic group is optionally substituted by a phenyl group which latter is optionally substituted by 1 to 3 substituent(s), wherein the substituent consists of a C₁₋₄ alkoxy group, or

R³ and R⁴ form, with the adjacent nitrogen atom and optionally with a further nitrogen atom or an oxygen atom, a saturated or unsaturated heterocyclic group having 5 or 6 members, being optionally substituted by a phenyl group that is optionally substituted by 1 to 3 substituents, wherein the substituent is a C₁₋₄ alkoxy group,

n has a value of 0, 1 or 2,

m has a value of 0, 1 or 2, or

A forms together with B a valence bond between the carbon atoms in positions 8 and 9, and in this case

R¹ represents a group of the formula

-CO-(CH₂)_p-R⁶, wherein

R⁶ stands for a halo atom, a phenoxy group, a C₁₋₄ alkoxy group or a group of the formula -NR⁷R⁸, wherein

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R⁷ and R⁸ mean, independently, a hydrogen atom, a guanyl group, a C₃₋₆ cycloalkyl group or a C₁₋₄ alkyl group which latter is optionally substituted by a phenyl group or a saturated heterocyclic group having 5 or 6 members and comprising one or more nitrogen atom(s) or a nitrogen and an oxygen atom as the heteroatom, wherein the phenyl group is optionally substituted by 1 to 3 identical or different substituent(s), wherein the substituent is a C₁₋₄ alkoxy group, or

R⁷ and R⁸ form together with the adjacent nitrogen atom an oxopyrrolidinyl group, a phthalimido group which latter is optionally substituted, or a saturated heterocyclic group having 5 or 6 members and comprising one or more nitrogen atom(s) or a nitrogen and an oxygen atom as the heteroatom, and said heterocyclic group is optionally substituted by 1 to 3 identical or different substituent(s) selected from the group consisting of a hydroxy group, a phenyl group, a phenoxy group, a phenyl(C₁₋₄ alkyl) group or a phenoxy(C₁₋₄ alkyl) group, wherein in case of the substituents listed the phenyl or phenoxy group is

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group, or
R³ and R⁴ form, together with the adjacent
nitrogen atom and optionally a further
nitrogen atom or oxygen atom, an imidazolyl,
morpholino or piperazinyl group, wherein
the piperazinyl group is substituted by
a methoxyphenyl group,
n has a value of 0 or 1,
m has a value of 0 or 1,
R² stands for a nitro group or an amino group,
A represents a hydrogen atom,
B means a hydrogen atom,
or a pharmaceutically suitable acid addition
salt thereof as the active ingredient.

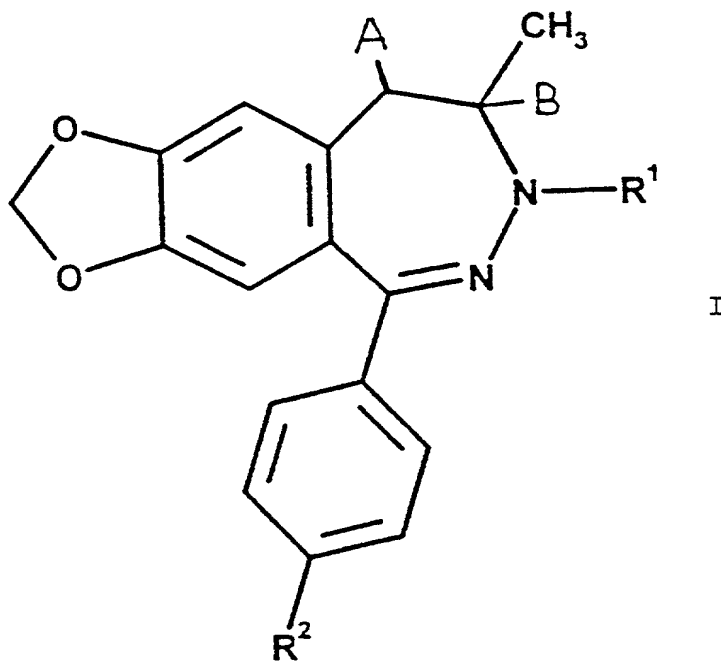
12. A pharmaceutical composition as
claimed in Claim 11 comprising a 1,3-dioxolo-
/4,5-h//2,3/benzodiazepine derivative of the
formula I, wherein

R³ represents a hydrogen atom,
R⁴ stands for a cyclopropyl group, a methoxy
group or an amino group,
n has a value of 0,
m has a value of 0,
R² means an amino group,
A represents a hydrogen atom,
B means a hydrogen atom,
or a pharmaceutically suitable acid addition
salt thereof as the active ingredient.

13. A pharmaceutical composition as
claimed in Claim 9 comprising an 8-methyl-
-7H-1,3-dioxolo/4,5-h//2,3/benzodiazepine
derivative of the formula I, wherein

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wherein

A represents a hydrogen atom,

B means a hydrogen atom,

R¹ stands for a group of the formula

$-(CH_2)_n-CO-(CH_2)_m-R$, wherein

R represents a halo atom, a pyridyl group or a group of the formula $-NR^3R^4$, wherein R³ and R⁴ mean, independently, a hydrogen atom, a C₃₋₆ cycloalkyl group, a C₁₋₄ alkoxy group, an amino group, a phenyl group optionally substituted by one or two C₁₋₄ alkyl group(s), a C₁₋₄ alkyl group which latter is optionally substituted by a phenyl group or a saturated heterocyclic group having 5 or 6 members and

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which latter is optionally substituted by a phenyl group or a saturated heterocyclic group having 5 or 6 members and comprising one or more nitrogen atom(s) or a nitrogen and an oxygen atom as the heteroatom, wherein the phenyl group is optionally substituted by 1 to 3 identical or different substituent(s), wherein the substituent is a C₁₋₄ alkoxy group, or

R⁷ and R⁸ form together with the adjacent nitrogen atom an oxopyrrolidinyl group, a phthalimido group which latter is optionally substituted, or a saturated heterocyclic group having 5 or 6 members and comprising one or more nitrogen atom(s) or a nitrogen and an oxygen atom as the heteroatom, and said heterocyclic group is optionally substituted by 1 to 3 identical or different substituent(s) selected from the group consisting of a hydroxy group, a phenyl group, a phenoxy group, a phenyl(C₁₋₄ alkyl) group or a phenoxy(C₁₋₄ alkyl) group, wherein in case of the substituents listed the phenyl or phenoxy group is optionally substituted by 1 to 3 identical or different substituent(s), wherein the substituent is a halo

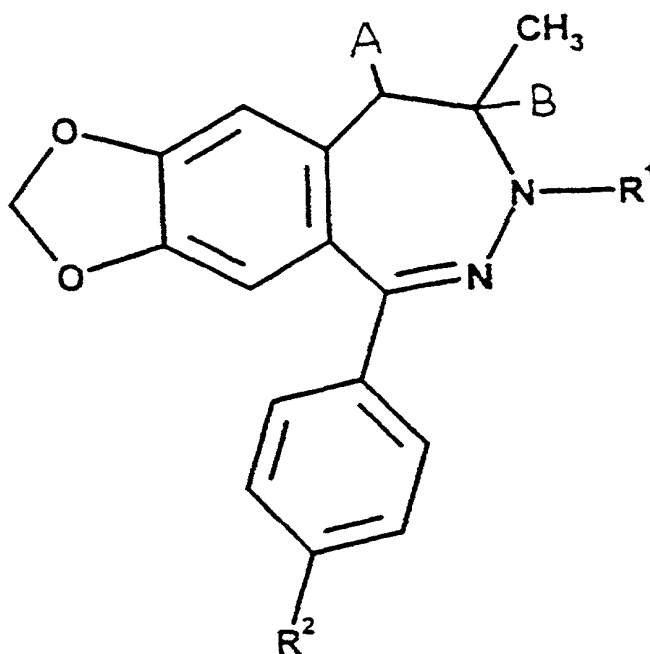
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atom or a C_{1-4} alkoxy group, and,
in case of the phenoxy(C_{1-4} alkyl)
group, the alkyl group is optionally
substituted by 1 or 2 hydroxy
group(s),

p has a value of 0, 1 or 2,
 R^2 stands for a nitro group, an amino group
or a (C_{1-4} alkanoyl)amino group,
or a pharmaceutically suitable acid addition
salt thereof.

17. A process for preparing a
pharmaceutical composition suitable for the
treatment of especially epilepsy, a neuro-
degenerative disease or a state after stroke,
characterized in that a 1,3-dioxolo/4,5-h/-
/2,3/benzodiazepine derivative of the formula
I



I

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is optionally substituted by 1 to 3 substituents, wherein the substituent is a C₁₋₄ alkoxy group, n has a value of 0, 1 or 2, m has a value of 0, 1 or 2, or

A forms together with B a valence bond between the carbon atoms in positions 8 and 9, and in this case

R¹ represents a group of the formula

-CO-(CH₂)_p-R⁶, wherein

R⁶ stands for a halo atom, a phenoxy group,

a C₁₋₄ alkoxy group or a group of the formula -NR⁷R⁸, wherein

R⁷ and R⁸ mean, independently, a hydrogen atom, a guanyl group, a C₃₋₆ cycloalkyl group or a C₁₋₄ alkyl group which latter is optionally substituted by a phenyl group or a saturated heterocyclic group having 5 or 6 members and comprising one or more nitrogen atom(s) or a nitrogen and an oxygen atom as the heteroatom, wherein the phenyl group is optionally substituted by 1 to 3 identical or different substituent(s), wherein the substituent is a C₁₋₄ alkoxy group, or

R⁷ and R⁸ form together with the adjacent nitrogen atom an oxopyrrolidinyl group, a phthalimido group which latter is optionally substituted, or a saturated heterocyclic group

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I hereby appoint the following attorneys to prosecute this application and/or an international application based on this application and to transact all business in the Patent and Trademark Office connected therewith and in connection with the resulting patent based on instructions received from the entity who first sent the application papers to the attorneys identified below, unless the inventor(s) or assignee provides said attorneys with a written notice to the contrary:

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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 Insert Date This Document is Signed
 Insert Residence
 Insert Citizenship

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 see above

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 (Revised 7-93)

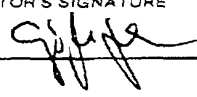
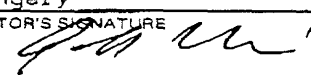
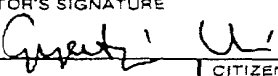
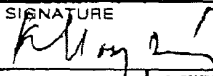
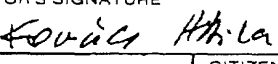
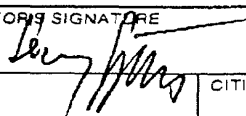
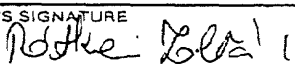
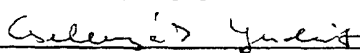
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Full Name of Inventor, if any: see above	GIVEN NAME <u>György</u> FAMILY NAME <u>LÉVAY</u>	INVENTOR'S SIGNATURE 	*DATE 04/25/2000
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Full Name of Inventor, if any: see above	GIVEN NAME <u>Zoltán</u> FAMILY NAME <u>RÁTKAI</u>	INVENTOR'S SIGNATURE 	*DATE 04/25/2000
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Full Name of Inventor, if any: see above	GIVEN NAME <u>Judit</u> FAMILY NAME <u>CSELENYÁK</u>	INVENTOR'S SIGNATURE 	*DATE 04/25/2000
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GIVEN NAME <u>14-00</u>	FAMILY NAME <u>SERES</u>	INVENTOR'S SIGNATURE <u>[Signature]</u>	DATE <u>04/25/2000</u>
RESIDENCE (City, State & Country) <u>Budapest, Hungary HUX</u>		CITIZENSHIP <u>Hungarian</u>	
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GIVEN NAME <u>15-00</u>	FAMILY NAME <u>SIMIG</u>	INVENTOR'S SIGNATURE <u>[Signature]</u>	DATE <u>04/25/2000</u>
RESIDENCE (City, State & Country) <u>Budapest, Hungary HUX</u>		CITIZENSHIP <u>Hungarian</u>	
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GIVEN NAME <u>16-00</u>	FAMILY NAME <u>SIMÓ</u>	INVENTOR'S SIGNATURE <u>[Signature]</u>	DATE <u>04/25/2000</u>
RESIDENCE (City, State & Country) <u>Budapest, Hungary HUX</u>		CITIZENSHIP <u>Hungarian</u>	
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GIVEN NAME <u>17-00</u>	FAMILY NAME <u>SZABADOS</u>	INVENTOR'S SIGNATURE <u>[Signature]</u>	DATE <u>04/25/2000</u>
RESIDENCE (City, State & Country) <u>Budapest, Hungary HUX</u>		CITIZENSHIP <u>Hungarian</u>	
POST OFFICE ADDRESS (Complete Street Address including City, State & Country) <u>2 Dombtető u., Budapest, H-1108, Hungary</u>			
GIVEN NAME <u>18-00</u>	FAMILY NAME <u>SZABO</u>	INVENTOR'S SIGNATURE <u>[Signature]</u>	DATE <u>04/25/2000</u>
RESIDENCE (City, State & Country) <u>Budapest, Hungary HUX</u>		CITIZENSHIP <u>Hungarian</u>	
POST OFFICE ADDRESS (Complete Street Address including City, State & Country) <u>25 Hold u., Budapest, H-1054, Hungary</u>			
GIVEN NAME <u>19-00</u>	FAMILY NAME <u>TIHANYI</u>	INVENTOR'S SIGNATURE <u>[Signature]</u>	DATE <u>04/25/2000</u>
RESIDENCE (City, State & Country) <u>Budapest, Hungary</u>		CITIZENSHIP <u>Hungarian</u>	
POST OFFICE ADDRESS (Complete Street Address including City, State & Country) <u>37 Postamester u., Budapest, H-1171, Hungary</u>			
GIVEN NAME <u>20-00</u>	FAMILY NAME <u>VEGH</u>	INVENTOR'S SIGNATURE <u>[Signature]</u>	DATE <u>04/25/2000</u>
RESIDENCE (City, State & Country) <u>Budapest, Hungary HUX</u>		CITIZENSHIP <u>Hungarian</u>	
POST OFFICE ADDRESS (Complete Street Address including City, State & Country) <u>89 Szondy u., Budapest, H-1068, Hungary</u>			
GIVEN NAME	FAMILY NAME	INVENTOR'S SIGNATURE	DATE
RESIDENCE (City, State & Country)		CITIZENSHIP	
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COMBINED DECLARATION AND POWER OF ATTORNEY FOR PATENT AND DESIGN APPLICATIONS

ATTORNEY DOCKET NO.
1060-136P

PLEASE NOTE:
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Insert Title



Check Box If
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As a below named inventor, I hereby declare that: my residence post office address and citizenship are as stated next to my name; that I verily believe that I am the original, first and sole inventor (if only one inventor is named below) or a joint inventor (if plural inventors are named below) of the subject matter which is claimed and for which a patent is sought on the invention entitled: * "1,3-Dioxolo/4,5-H//2,3/benzodiazepine derivatives as
Ampa/Kainate receptor inhibitors"

the specification of which is attached hereto unless one of the following boxes is checked:

- ☐ The Specification was filed on _____ and was assigned
Serial No. _____ and was amended on _____
☒ was filed as PCT international application number PCT/HU98/00076 on
August 7, 1998 and was amended under PCT Article 19 on _____

(if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I do not know and do not believe the same was ever known or used in the United States of America before my or our invention thereof, or patented or described in any printed publication in any country before my or our invention thereof, or more than one year prior to this application, that the same was not in public use or on sale in the United States of America more than one year prior to this application, that the invention has not been patented or made the subject of an inventor's certificate issued before the date of this application in any country foreign to the United States of America on an application filed by me or my legal representatives or assigns more than twelve months (six months for designs) prior to this application, and that no application for patent or inventor's certificate on this invention has been filed in any country foreign to the United States of America prior to this application by me or my legal representatives or assigns, except as follows:

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below:

Prior Foreign Application(s)

Priority Claimed

Insert Priority
Information
(if appropriate)



<u>P 97 01382</u> (Number)	<u>Hungary</u> (Country)	<u>August 12, 1997</u> (Month/Day/Year Filed)	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
<u>P 97 01383</u> (Number)	<u>Hungary</u> (Country)	<u>August 12, 1997</u> (Month/Day/Year Filed)	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
_____ (Number)	_____ (Country)	_____ (Month/Day/Year Filed)	<input type="checkbox"/> Yes	<input type="checkbox"/> No
_____ (Number)	_____ (Country)	_____ (Month/Day/Year Filed)	<input type="checkbox"/> Yes	<input type="checkbox"/> No
_____ (Number)	_____ (Country)	_____ (Month/Day/Year Filed)	<input type="checkbox"/> Yes	<input type="checkbox"/> No
_____ (Number)	_____ (Country)	_____ (Month/Day/Year Filed)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

All Foreign Applications, if any, for any Patent or Inventor's Certificate Filed More Than 12 Months (6 Months for Designs) Prior To The Filing Date of This Application:

Country	Application No	Date of Filing (Month/Day/Year)
_____	_____	_____
_____	_____	_____

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56 which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

_____ (Application Serial No.)	_____ (Filing Date)	_____ (Status — patented, pending, abandoned)
_____ (Application Serial No.)	_____ (Filing Date)	_____ (Status — patented, pending, abandoned)

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